

The Impact of the APOE ϵ 4 on the Number of Neurons and Gene Expression of Degenerating Neurons in the Dorsolateral Prefrontal Cortex in Alzheimer's Patients

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Abstract

Alzheimer's disease (AD) is highly prevalent in the elderly population and leads to AD patients' higher mortality, low life quality, and lead to a huge economic burden on the health system. Even though the APOE ϵ 4 gene has been identified as a risk factor for the late onset of AD, there are no studies to examine the impact of APOE ϵ 4 on the neural and gene expression mechanisms of cognitive impairment in AD. Our study examined the impact of APOE ϵ 4 on AD patients' cognitive function and the level of a hallmark of AD pathology. This study also examined the impact of APOE ϵ 4 on the number of neurons in the dorsolateral prefrontal cortex (DLPFC) and the gene expression of degenerating neurons. This study used data from one publicly available dataset called the Seattle Alzheimer's Disease Brain Cell Atlas consortium (SEA-AD), including 75 AD patients ($M = 88.56$ years, $SD = 7.89$). T-tests revealed a significant difference in participants' age at death, cognitive status, age of onset cognitive symptoms, cognitive abilities screening instrument score, mini-mental state examination score, montreal cognitive assessment score, and the percentage of Sst chodl, L6 b, and L5/6 NP cells between APOE ϵ 4 carriers and non-carriers. Single-cell RNA sequence revealed that APOE ϵ 4 led to a significantly less gene expression of the GLRA1 gene in Sst chodl neurons and KCNA1 gene in L5/6 NP neurons. The present findings provide insight for enhancing understanding of the cause of AD and AD's cognitive impairment from an APOE ϵ 4 perspective.

Keywords

Alzheimer's Disease, APOE ϵ 4, Cognitive Impairment, Differential Gene Expression, Single-Cell RNA Sequence

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is related to the most common cause of dementia, accounting for about 60% - 80% of these cases [1]. It is estimated that nearly 1 million new cases are diagnosed each year [2]. The treatment of AD imposes a huge burden on the health system, with nearly \$600 million per year [3]. AD is characterized by memory loss and cognitive impairment, which reduce the elderly population's normal daily function, increase dependence on people, and even impact the mortality of the elderly population [4] [5]. Nearly 33 % of the elderly population over 65 years old died due to suffering from AD and dementia [6]. Pathologically, the hallmarks and risk factors related to AD include the increase of amyloid plaques caused by the accumulation of amyloid- β ($A\beta$) peptide, the increase of neurofibrillary tangles (NFTs) caused by the deposition of phosphorylated tau, as well as synaptic dysfunction, inflammation [7]-[9].

Genetic risk factors impact these pathogenic pathways related to late-onset AD (LOAD) and thus increase the risk for AD [10]. The strongest risk factor for LOAD is apolipoprotein E (apoE), with three predominant APOE alleles [11]. Among these three predominant APOE alleles, $\epsilon 4$ (APOE $\epsilon 4$) alleles are considered a significant risk factor for developing AD [12] [13]. People with APOE $\epsilon 4$ experience a higher risk of suffering from dementia and poorer cognitive function [14]-[16]. Individuals with APOE $\epsilon 4$ show earlier accumulation of $A\beta$ and increased $A\beta$ levels than noncarriers [17]-[20]. The frequency of APOE $\epsilon 4$ is also significantly higher in AD patients than in healthy populations [21]. Additionally, APOE $\epsilon 4$ compromises $A\beta$ clearance by disrupting receptor-mediated clearance and proteolytic degradation [22] [23]. This results in increased $A\beta$ deposition in APOE $\epsilon 4$ carriers, leading to synaptic dysfunction, synaptic loss, cognitive impairment, and a higher risk of AD [24]-[26]. In addition, APOE $\epsilon 4$ carriers show increased phosphorylated tau deposition compared to noncarriers, regardless of the presence of $A\beta$ [27], which further exacerbates synaptic dysfunction and neurodegeneration, leading to a higher risk of AD [28] [29].

APOE $\epsilon 4$ is associated with neurodegeneration and interruption of the normal neuron function, contributing to AD. APOE $\epsilon 4$ promotes $A\beta$ accumulation [17]-[20], which could interfere with ion channels critical for synaptic transmission [30]-[33]. Dysfunctional ion channels may lead to synapse loss in AD [34]-[36]. Thus, APOE $\epsilon 4$ may be one reason leading to the number of neurons declining in AD patients and cognitive impairment [37] [38]. However, there is no direct evidence to show the impact of APOE $\epsilon 4$ on the number of neurons and on the gene expression in specific neurons.

Given the high mortality and prevalence, low life quality, and huge economic burden related to AD [3]-[6], understanding gene factors related to AD is important to enhance the understanding of the mechanisms of underlying the cause of AD. Despite literature suggesting APOE $\epsilon 4$ is related to AD and increases the accumulation of $A\beta$, little is known about the impact of APOE $\epsilon 4$ on neuron neu-

roderegeneration and whether APOE ϵ 4 influences gene expression in these neurons. This current study aims to explore the impact of APOE ϵ 4 on cognitive function, the level of hallmarks of pathology related to AD, the number of neurons, and gene expression related to these neurons. Hypothesis 1: Compared with APOE ϵ 4 non-carriers, APOE ϵ 4 carriers will have a significantly younger age at death, younger age of onset AD, younger age of dementia diagnosis, and lower score in cognitive function test. Hypothesis 2: Compared with APOE ϵ 4 non-carriers, APOE ϵ 4 carriers will have a significantly decreased number of neurons in the prefrontal cortex.

2. Materials and Method

This study used the Seattle Alzheimer's disease Brain Cell Atlas consortium (SEA-AD) [39], which is a publicly available dataset, including 85 participants' information (including 75 AD patients and 10 healthy participants) on AD pathology, cognitive condition, whether are APOE ϵ 4 carriers, cell types in the dorsolateral prefrontal cortex (DLPFC), and single-nucleus RNA sequence. This study used 75 AD patients' information about AD pathology, AD patients' cognitive condition, AD's life span, and AD patients' APOE ϵ 4 information (APOE ϵ 4 carriers and APOE ϵ 4 non-carriers) to investigate the impact of APOE ϵ 4 on AD's cognitive function and pathology. Then, this study used AD patients' information about the number of neurons in the DLPFC, a brain region related to working memory and executive function [40], to explore the role of APOE ϵ 4 in different neurons. To investigate the impact of APOE ϵ 4 on gene expression of specific cell types, the current study used a single-nucleus RNA sequence.

3. Bioinformatics Tools

The calculation of the percentage of different cell types in DLPFC was done in Python (3.12.2). The statistics tests on the impact of APOE ϵ 4 on various factors were done in R studio (v 4.4.2). In addition, the human motor cortex is used as the reference to analyze the single-cell RNA sequence by using the Seurat toolbox in R [41].

4. Results

4.1. Descriptive Statistics

Participant characteristics are described in **Table 1**. A total of $N = 75$ participants were included in this study, of which 46 were female with an average age at death of 89, and 29 were male with an average age at death of 88.

4.2. The Impact of APOE ϵ 4 Gene on AD Patient's Cognitive Function

Several *t*-tests were conducted to examine whether there was a significant difference between APOE ϵ 4 carriers and non-carriers in participants' age at death, cognitive status, age of onset cognitive symptoms, cognitive abilities screening instrument score, mini-mental state examination score, and montreal cognitive assess-

ment score. The significant difference between APOE ϵ 4 carriers and non-carriers that have significant P values (<0.05) and effect sizes (Cohen's d) is shown in **Figure 1** and **Table 2**.

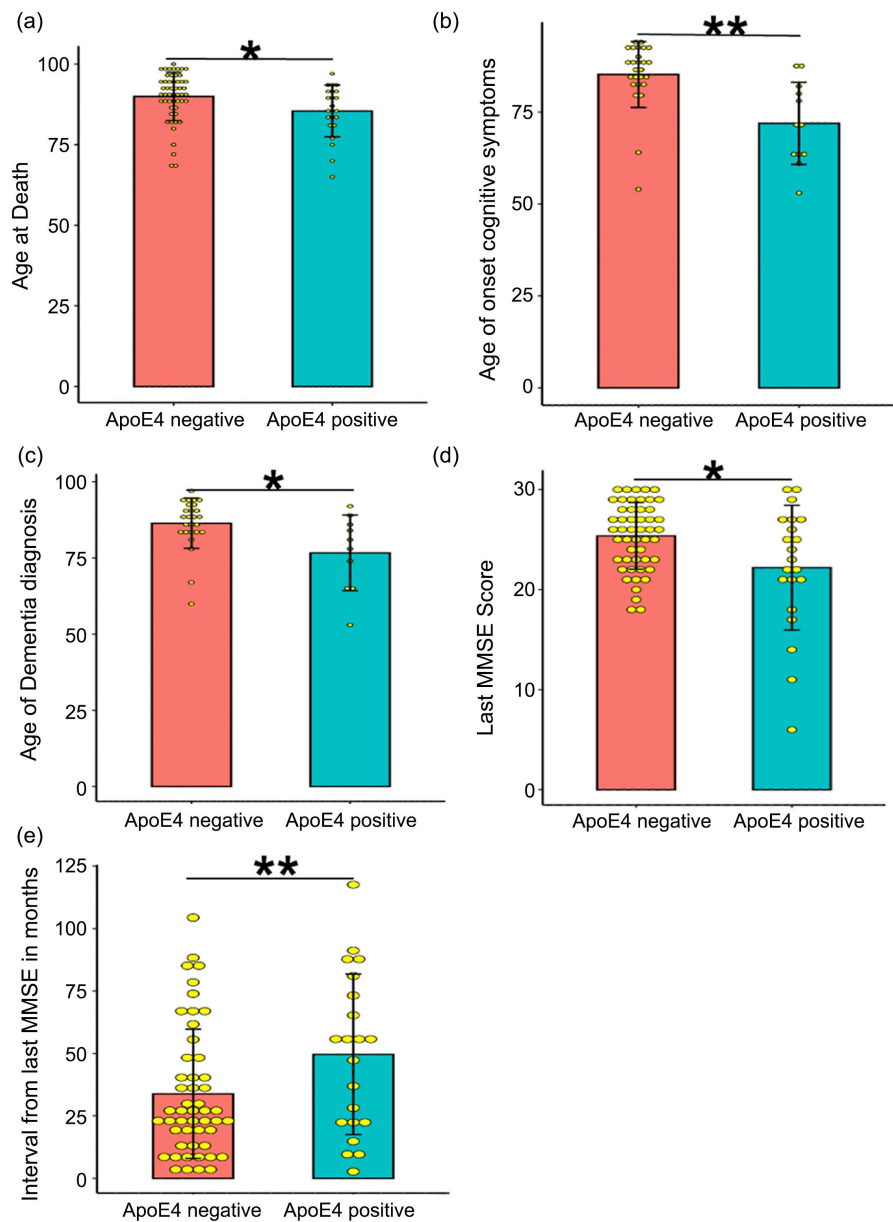


Figure 1. The P-value of the Effect of the APOE ϵ 4 on Cognitive Function. *Note:* From (a)-(e), *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. N = 52 for the APOE ϵ 4 non-carriers and N = 23 for the APOE ϵ 4 carriers. ApoE4 positive indicates APOE ϵ 4 carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers. (a) bar plot shows the difference in Age at Death between APOE ϵ 4 carriers and non-carriers. (b) bar plot shows the difference in Age of Onset Cognitive Symptoms between APOE ϵ 4 carriers and non-carriers. (c) bar plot shows the difference in Age of Dementia Diagnosis between APOE ϵ 4 carriers and non-carriers. (d) bar plot shows the difference in the Last MMSE Score between APOE ϵ 4 carriers and non-carriers. (e) bar plot shows the difference in the Interval from the last MMSE in months between APOE ϵ 4 carriers and non-carriers.

Table 1. Descriptive statistics of participant characteristics.

		Mean (SD)	Range
Age at death		88.56 (7.89)	35
Sex	Female	46 (61.3%)	\
	Male	29 (38.7%)	\
APOE ϵ 4	Carriers	23 (31%)	\
	Non-carriers	52 (69%)	\
Cognitive Status	Dementia	42 (56%)	\
	No Dementia	33 (44.0%)	\
Age of Onset Cognitive Symptoms		81.00 (11.42)	41
CASI Score		86.80 (9.60)	33
MMSE Score		24.42 (4.58)	24
MOCA Score		18.21 (6.47)	21
Year of Education		16.29 (2.78)	9

Note. CASI Score: The Cognitive Abilities Screening Instrument. MMSE Score: Mini-Mental State Examination. MOCA Score: Montreal Cognitive Assessment.

Table 2. The effect size of the impact of the APOE ϵ 4 on cognitive function.

	APOE ϵ 4 carriers		APOE ϵ 4 non-carriers		<i>df</i>	<i>t</i>	Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Age at Death	85.43	7.98	89.97	7.52	38.64	2.34	0.58
Age of Onset Cognitive Symptoms	71.92	11.17	85.19	8.96	17.81	3.61	1.37
Age of Dementia Diagnosis	76.70	12.42	86.42	8.27	12.21	2.29	1.02
Last MMSE Score	49.65	6.23	25.53	3.34	24.08	2.34	0.66
Interval from Last MMSE in Months	22.19	32.14	32	25.88	28.94	-2.29	0.79

4.3. The Impact of APOE ϵ 4 on AD Patient's Pathology

Several *t*-tests were conducted to examine whether there was a significant difference between APOE ϵ 4 carriers and non-carriers in participants' number of AT8 positive cells (τ), 6e10 positive cells ($A\beta$), 1ba1 and 6e10 positive cells ($A\beta$), hematoxylin positive nuclei, and glial fibrillary acidic protein (GFAP). The significant difference between APOE ϵ 4 carriers and non-carriers that have significant P values (<0.05) and effect sizes (Cohen's *d*) is shown in **Figure 2** and **Table 3**. The significant difference in these hallmarks of AD pathology in specific cerebral cortex layers 1 - 5 between APOE ϵ 4 carriers and non-carriers that have significant P values (<0.05) is shown in **Figure 3**.

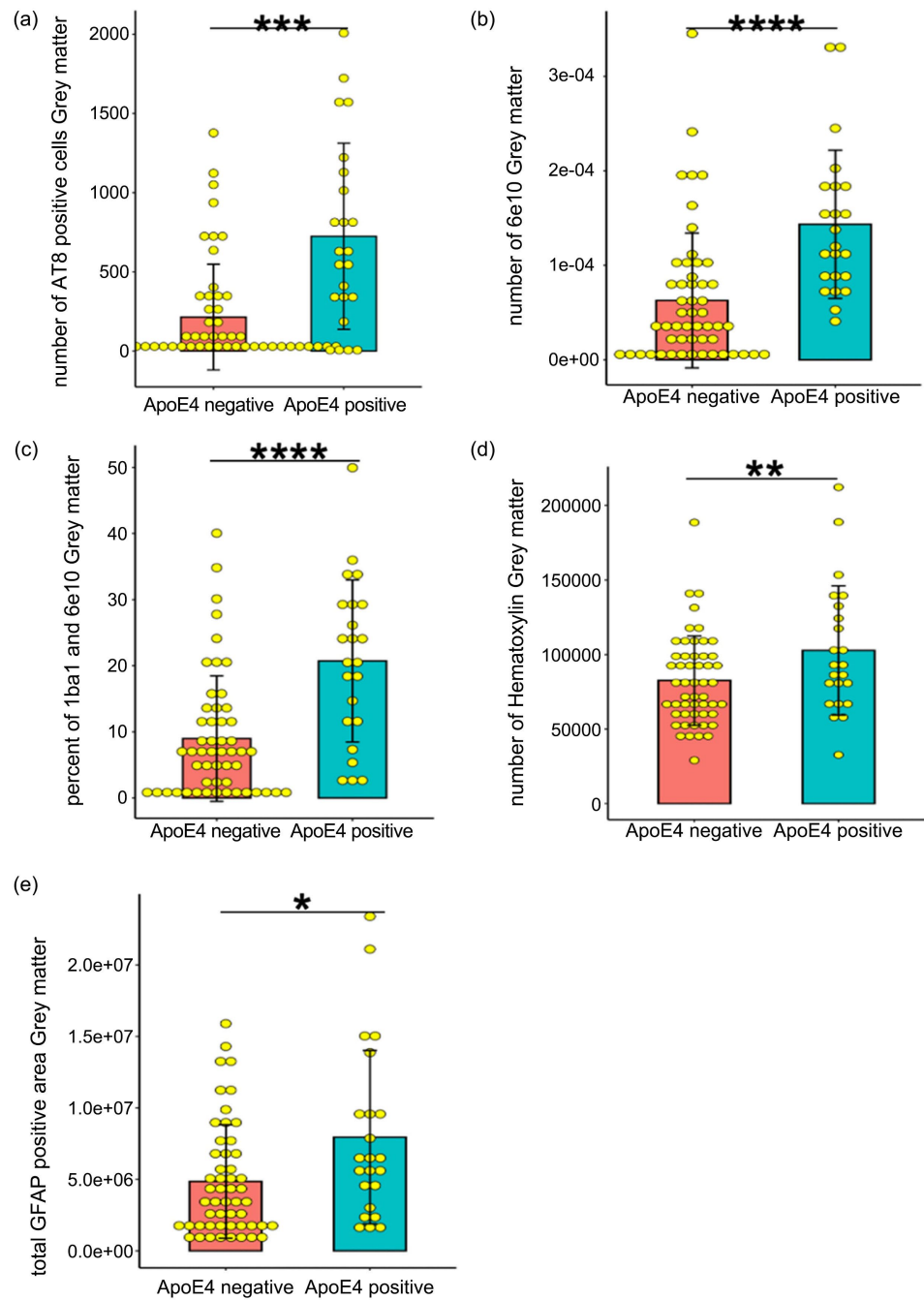
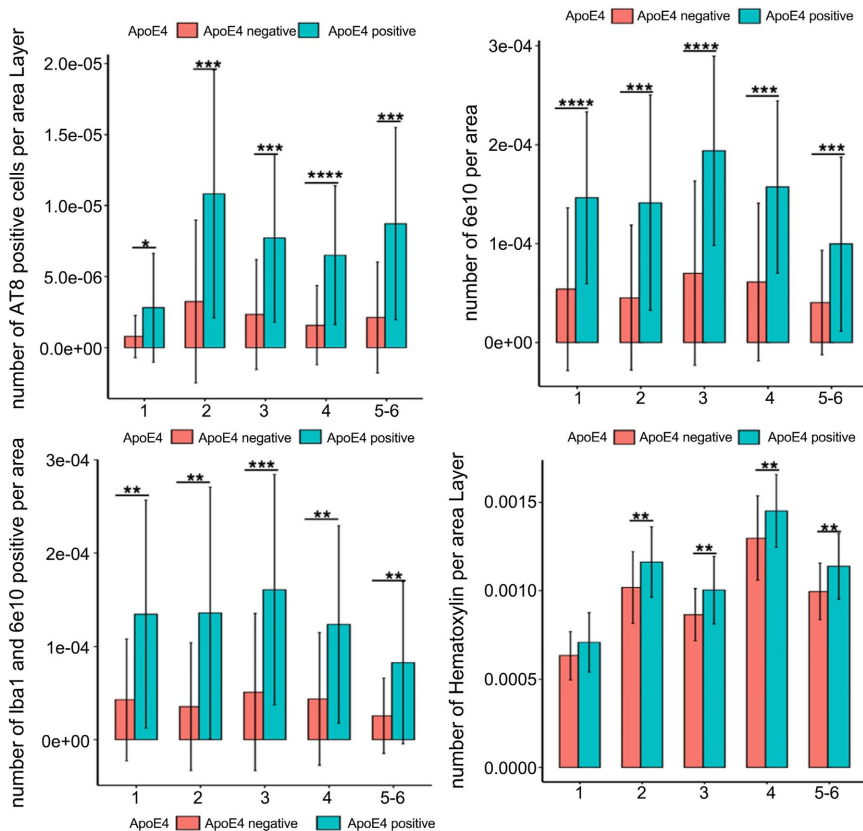


Figure 2. The P-value of the Impact of APOE ϵ 4 on AD Pathology in Grey Matter. *Note.* From a-e, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. N = 52 for the APOE ϵ 4 non-carriers and N = 23 for the APOE ϵ 4 carriers. ApoE4 positive indicates APOE ϵ 4 carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers. (a) The bar plot shows the difference in the number of AT8 positive cells in the grey matter of APOE ϵ 4 carriers and non-carriers. (b) bar plot shows the difference in the number of 6e10 positive objects grey matter between APOE ϵ 4 carriers and non-carriers. (c) bar plot shows the difference in the number of Iba1 and 6e10 positive co-localized objects grey matter between APOE ϵ 4 carriers and non-carriers. (d) bar plot shows the difference in the number of hematoxylin-positive nuclei grey matter between APOE ϵ 4 carriers and non-carriers. (e) bar plot shows the difference in the total of glial fibrillary acidic protein (GFAP) grey matter between APOE ϵ 4 carriers and non-carriers.

Table 3. The effect size of the impact of APOE ϵ 4 on AD pathology in grey matter.

	APOE ϵ 4 carriers		APOE ϵ 4 non-carriers		<i>df</i>	<i>t</i>	Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Number of AT8 Positive Cells Grey Matter	724.21	597.33	185.89	335.21	26.94	-4.17	1.32
Number of 6e10 Grey Matter	13822.30	9901.74	5091.69	9113.34	35.27	-3.73	0.97
Percent of Iba1 and 6e10 Grey Matter	20.72	12.26	7.68	9.49	32.05	-4.62	1.28
Number of Hematoxylin Grey Matter	102729.96	43364.31	80940.33	29973.8	29.36	-2.24	0.66
Total GFAP Positive Area Grey Matter	7955801	6064636.58	4530796	3966739.33	28.74	-2.53	0.76



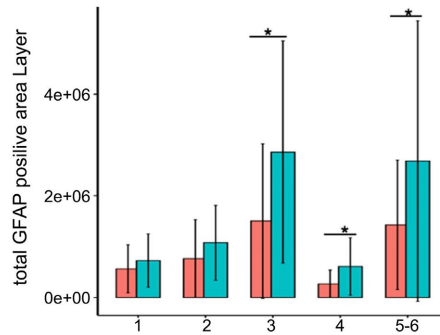


Figure 3. The Impact of APOE ϵ 4 on AD Pathology in Cerebral Cortex Layers 1-5. *Note.* From (a)-(g), *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. N = 52 for the APOE ϵ 4 non-carriers and N = 23 for APOE ϵ 4 carriers. ApoE4 positive indicates APOE ϵ 4 carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers. (a) bar plot shows the difference in the average 6e10 positive objects in cerebral cortex layers 1 - 5 between APOE ϵ 4 carriers and non-carriers. (b) bar plot shows the difference in the percent of 6e10 positive colocalized objects grey matter in cerebral cortex layers 1 - 5 between APOE ϵ 4 carriers and non-carriers. (c) bar plot shows the difference in the number of Iba1 and 6e10 positive colocalized objects per area grey matter in cerebral cortex layers 1 - 5 between APOE ϵ 4 carriers and non-carriers. (d) bar plot shows the difference in the number of Hematoxylin positive nuclei grey matter in cerebral cortex layers 1 - 5 between APOE ϵ 4 carriers and non-carriers. (e) bar plot shows the difference in total GFAP positive area grey matter in cerebral cortex layers 1-5 between APOE ϵ 4 carriers and non-carriers.

4.4. The Impact of APOE ϵ 4 on the Proportion of Neurons in Prefrontal Cortex

Several *t*-tests were conducted to examine whether there was a significant difference in the proportion of neurons between APOE ϵ 4 carriers and non-carriers, including L2/3 IT (Layer 2/3 intra-telencephalic), L5 IT, L4 IT, Sst (somatostatin), L6b, L6 CT (corticothalamic), Lamp5Lhx6, OPC (oligodendrocyte precursor cells), Pvalb (parvalbumin), Vip (vasoactive intestinal polypeptide), L6 IT Car3, L6 IT, Sncg (synuclein gamma), MicrogliaPVM (perivascular macrophages), Pax6, L5 ET (extra-telencephalic projecting), Chandler, Sst Chodl, VLMC (vascular and leptomeningeal cells), Endothelial, Oligodendrocyte, L5/6 NP (near-projecting), lamp5, and Astrocyte. APOE ϵ 4-carriers have a lower proportion of L6b, Sst Chodl, and L5/6 NP than APOE ϵ 4 non-carriers, with significant P values (<0.05), and effect size (Cohen's) as shown in **Figure 4** and **Table 4**.

4.5. The Impact of APOE ϵ 4 on the Gene Expression of Degenerating Neurons

The single-cell RNA sequence was conducted to examine whether there was a significant difference in gene expression related to ion channels in Sst chodl, L6 b, and L5/6 NP cells between APOE ϵ 4-carriers and non-carriers. In Sst chodl, GLRA1 gene controlling Glycine receptors was found to have significantly less gene expression in APOE ϵ 4-carriers than in APOE ϵ 4 non-carriers, with P = 0.04 < 0.05. In L6 b, there was no gene expression difference related to ion channels between APOE ϵ 4 carriers and non-carriers. In L5/6 NP cells, KCNA1 gene controlling potassium voltage ion channels was found to have significantly less gene

expression in the APOE ϵ 4 carriers than in the APOE ϵ 4 non-carriers, as shown in **Figure 5** and **Figure 6**.

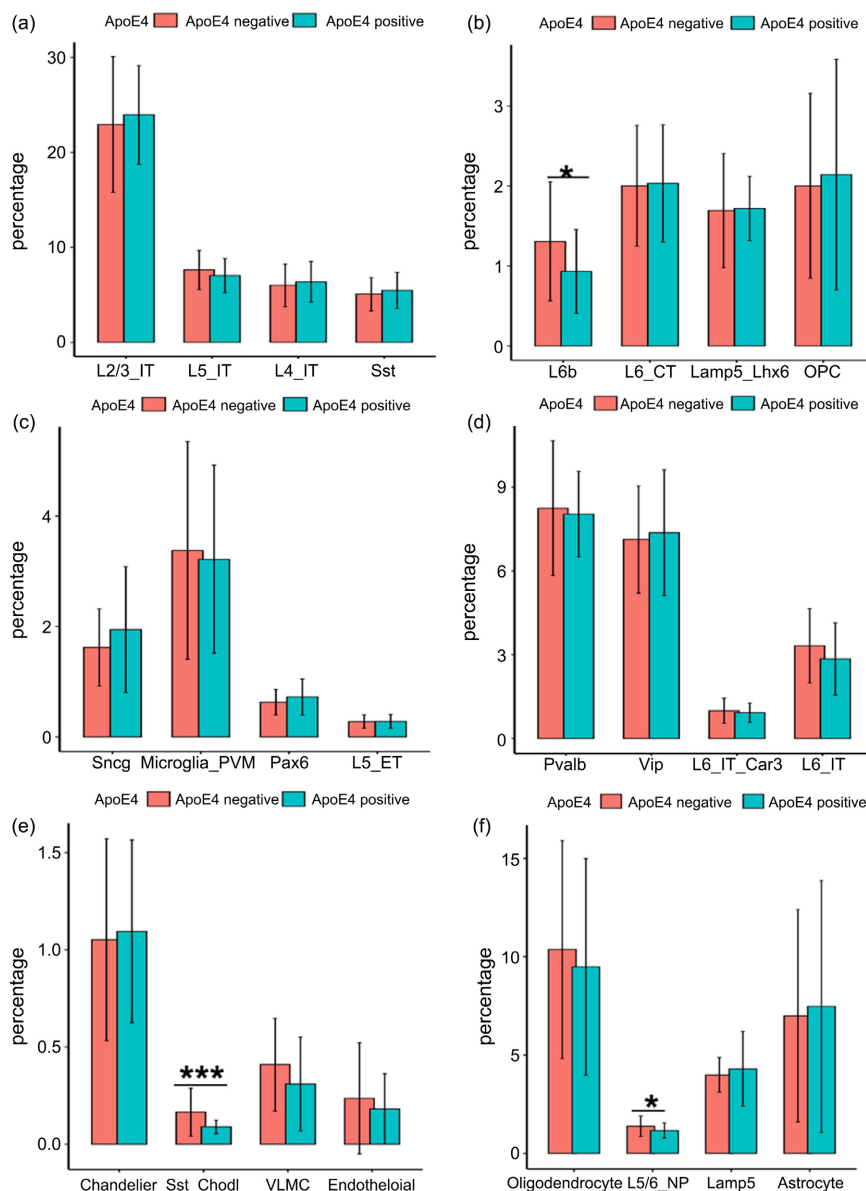


Figure 4. The P-value of the Impact of the APOE ϵ 4 on the Proportion of Neurons. *Note.* From (a)-(f), *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. N = 52 for the APOE ϵ 4-non carriers and N = 23 for the APOE ϵ 4-carriers. ApoE4 positive indicates APOE ϵ 4-carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers. (a) bar plot shows the difference proportion of L2/3 IT, L5 IT, L4 IT, and Sst cells between APOE ϵ 4-carriers and non-carriers. (b) bar plot shows the difference proportion of L6b, L6 CT, Lamp5Lhx6, and OPC cells between APOE ϵ 4-carriers and non-carriers. (c) bar plot shows the difference proportion of Pvalb, Vip, L6 IT Car3, and L6 IT cells between APOE ϵ 4-carriers and non-carriers. (d) bar plot shows the difference proportion of Sncg, MicrogliaPVM, Pax6, and L5 ET cells between APOE ϵ 4-carriers and non-carriers. (e) bar plot shows the difference proportion of Chandler, Sst Chodl, VLMC and Endothelial cells between APOE ϵ 4-carriers and non-carriers. f. bar plot shows the difference proportion of Oligodendrocyte, L5/6 NP, lamp5, and Astrocyte cells between APOE ϵ 4-carriers and non-carriers.

Table 4. The effect size of the impact of the APOE ϵ 4 on the proportion of neurons.

Neuron	APOE ϵ 4 carriers		APOE ϵ 4 non-carriers		<i>df</i>	<i>t</i>	Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
L6 b	0.93	0.53	1.31	0.74	50.25	2.49	0.54
Sst Chodl	0.09	0.03	0.16	0.12	70.41	4.13	0.70
L5/6 NP	1.17	0.38	1.39	0.52	48.49	2.04	0.45

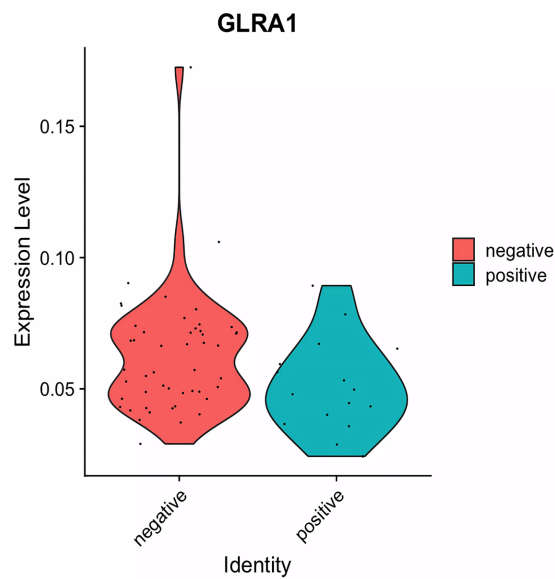


Figure 5. The Difference in GLRA1 Gene Expression between APOE ϵ 4 Carriers and Non-carriers. *Note.* ApoE4 positive indicates APOE ϵ 4 carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers.

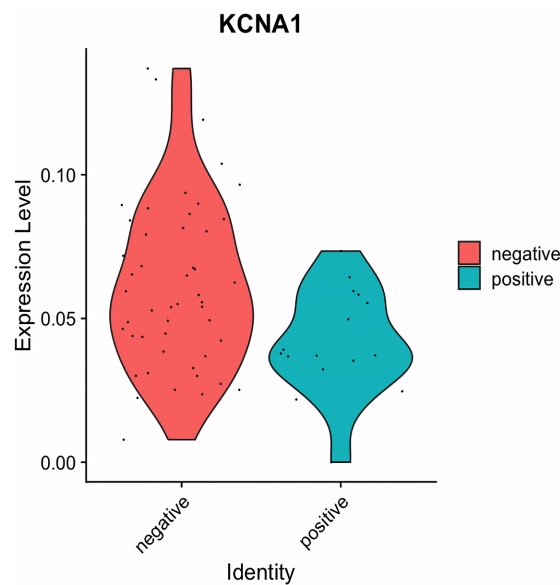


Figure 6. The Difference in KCNA1 Gene Expression between APOE ϵ 4 Carriers and Non-carriers. *Note.* ApoE4 positive indicates APOE ϵ 4 carriers, while ApoE4 negative indicates APOE ϵ 4 non-carriers.

5. Discussion

This study investigates the effect of APOE ϵ 4 on AD patients' cognitive function, AD pathology, the number of neurons in DLPFC, and gene expression of ion channels. Our findings suggest that APOE ϵ 4 is a factor leading to lower cognitive function and an increased risk of AD pathology. Specifically, APOE ϵ 4 is associated with a decline in Sst Chodl, L6b, and L5/6 NP neurons. In Sst Chodl neurons, APOE ϵ 4 reduce the expression of the glycine receptors gene, while in L5/6 NP neurons, APOE ϵ 4 reduce the expression of the potassium voltage ion channels (Kv1 channels) gene.

The present study highlights the relationship between the expression of APOE ϵ 4 and cognitive impairment, as well as the level of markers of AD pathology. The expression of APOE ϵ 4 is related to the increasing number of AT8 cells, 6e10 positive cells, 1ba1, 6e10 co-localized cells, and Glial fibrillary acidic protein (GFAP) in the prefrontal cortex. The findings align with previous studies [17]-[20] [27], indicating that APOE ϵ 4 carriers have a higher level of A β and tau. Additionally, the findings that APOE ϵ 4 carriers have a younger age at death, lower ability of cognitive function, and a younger age of onset of dementia are consistent with previous studies [14]-[16]. Overall, these findings validate the idea that APOE ϵ 4 increases the risk of AD from accumulation of A β and tau and reduces people's cognitive function.

This study shows a link between APOE ϵ 4 and neurodegeneration. Focusing on the cell-type-specific evidence, APOE ϵ 4 leads to damage in Sst Chodl, L5/6 near-projecting pyramidal neurons (L5/6 NP), and L6b neurons. These findings are consistent with previous studies that AD is accompanied by neurodegeneration of these neurons [37] [38]. Sst neurons regulate the degradation of A β [42], and the loss of Sst neurons in AD patients has been shown to be related to the accumulation of A β , which increases the risk of AD [37]. Sst Chodl is a subtype of Sst neuron, which is an inhibitory neuron [43] [44]. Similarly to Sst neurons, Sst Chodl neurons also degenerate in AD patients [38], and in this study, APOE ϵ 4 carriers are more likely to accumulate A β than APOE ϵ 4 non-carriers, indicating that Sst Chodl neurons may also have a similar function as Sst neurons to clearance of A β and APOE ϵ 4 lead to the degenerate of Sst Chodl neurons, resulting the accumulation of A β contributing to AD's cognitive impairment [37] [38]. L5/6 NP and L6b are neuronal glutamatergic neurons and thus play a role in releasing glutamate [45]. In this study, APOE ϵ 4 leads to damage in L5/6 NP and L6b and the accumulation of A β , leading to glutamatergic dysfunction, contributing to synapse loss, synapse toxicity, and cognitive impairment related to AD [34]-[36] [46]-[48].

This study uses single-cell RNA sequencing to explore how APOE ϵ 4 affects the gene expression in specific neuron types, including Sst Chodl and L5/6 near-projecting pyramidal neurons (L5/6 NP). In Sst Chodl neurons, APOE ϵ 4 was associated with reduced expression of the glycine receptors. Glycine receptors are crucial for neuronal inhibition, as their activation allows Cl⁻ ions to influx into the

postsynaptic membrane, hyperpolarizing it and reducing neuronal excitability [49] [50]. A decrease in glycine receptors weakens neuronal inhibition. Additionally, intracellular $A\beta$ has been linked to inhibition loss regulated by the glycine receptors [30]. Our study showed that APOE ϵ 4 promotes $A\beta$ deposition, which in turn decreases gene expression of glycine receptors in the Sst Chodl neurons, leading to reduced inhibition and increased neuronal excitability. This results in the imbalance between inhibition and excitability [30] [51], contributing to cognitive impairments related to AD [47] [48]. In addition, we found that in L5/6 NP neurons, APOE ϵ 4 carriers decrease the expression of potassium voltage ion channels (Kv1 channels). These channels play a critical role in regulating the action potential threshold, neuron excitability, and synaptic transmission [52]-[54]. Reduced Kv1 channel activity could increase the probability of neurotransmitter release [31]-[33]. The current study showed APOE ϵ 4 decreases gene expression of Kv1 channels, which may prompt L5/6 NP neurons to release glutamate. Additionally, APOE ϵ 4 carriers lead to $A\beta$ accumulation [17]-[20], interrupting the glutamate uptake and clearance [55] [56]. Together, APOE ϵ 4 decreases gene expression of Kv1 channels and prompts the accumulation of $A\beta$, which could elevate extracellular glutamate levels, resulting in excitotoxicity, synapse toxicity and synapse loss [34]-[36]. These downstream may lead to cognitive impairments observed in AD, consistent with previous studies [46]-[48] [57].

6. Conclusion

Our study demonstrates that APOE ϵ 4 contributes to cognitive impairment, shorter life span, and earlier onset of AD. The APOE ϵ 4 also leads to neurodegeneration related to AD in Sst cells, L5/6 NP, and L6b neurons. The APOE ϵ 4 decreases the gene expression of glycine receptors in Sst cells and the gene expression of potassium voltage ion channels in L5/6 NP, which is related to cognitive impairment in AD. The findings provided insight into how APOE ϵ 4 contributes to AD symptoms, neuronal loss, and altered gene expression. Our study strengthens the understanding of the cause of AD from a gene perspective and offers a new clue for the future intervention of AD, such as through enhancing and recovery of the function of ion channels to alleviate AD patients' cognitive impairment. However, this study only focused on the role of the APOE ϵ 4 in the prefrontal cortex. Different brain regions have different functions and have various amounts of different neurons [58]. Therefore, APOE ϵ 4 may have a different effect on the number of neurons between various brain regions. The damaged temporal cortex and parietal cortex are related to the early stage of AD [59] [60]. Hence, future studies should focus on the impact of APOE ϵ 4 on the temporal and parietal cortex neurons, particularly in the early stage of AD. Additionally, one limitation is the smaller sample size of APOE ϵ 4 carriers in the SEA-AD dataset, and thus, future studies should include more APOE ϵ 4 carriers to gain a more general understanding of the impact of APOE ϵ 4 on AD patients' cognitive impairment.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Alzheimer's Association (2016) Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia*, **12**, 459-509. <https://doi.org/10.1016/j.jalz.2016.03.001>
- [2] Alzheimer's Association (2024) Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, **20**, 3708-3821.
- [3] World Health Organization and Alzheimer's Disease International (2012) Dementia: A Public Health Priority.
- [4] Cass, S.P. (2017) Alzheimer's Disease and Exercise: A Literature Review. *Current Sports Medicine Reports*, **16**, 19-22. <https://doi.org/10.1249/ISR.0000000000000332>
- [5] Glenthøj, L.B., Jepsen, J.R.M., Hjorthøj, C., Bak, N., Kristensen, T.D., Wenneberg, C., *et al.* (2016) Negative Symptoms Mediate the Relationship between Neurocognition and Function in Individuals at Ultrahigh Risk for Psychosis. *Acta Psychiatrica Scandinavica*, **135**, 250-258. <https://doi.org/10.1111/acps.12682>
- [6] Barnes, J.N. (2015) Exercise, Cognitive Function, and Aging. *Advances in Physiology Education*, **39**, 55-62. <https://doi.org/10.1152/advan.00101.2014>
- [7] Guo, T., Zhang, D., Zeng, Y., Huang, T.Y., Xu, H. and Zhao, Y. (2020) Molecular and Cellular Mechanisms Underlying the Pathogenesis of Alzheimer's Disease. *Molecular Neurodegeneration*, **15**, Article No. 40. <https://doi.org/10.1186/s13024-020-00391-7>
- [8] de Ture, M.A. and Dickson, D.W. (2019) The Neuropathological Diagnosis of Alzheimer's Disease. *Molecular Neurodegeneration*, **14**, Article No. 32. <https://doi.org/10.1186/s13024-019-0333-5>
- [9] Serrano-Pozo, A., Frosch, M.P., Masliah, E. and Hyman, B.T. (2011) Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine*, **1**, a006189. <https://doi.org/10.1101/cshperspect.a006189>
- [10] Barber, R.C. (2012) The Genetics of Alzheimer's Disease. *Scientifica*, **2012**, 1-14. <https://doi.org/10.6064/2012/246210>
- [11] Wightman, D.P., Jansen, I.E., Savage, J.E., Shadrin, A.A., Bahrami, S., Holland, D., *et al.* (2021) A Genome-Wide Association Study with 1,126,563 Individuals Identifies New Risk Loci for Alzheimer's Disease. *Nature Genetics*, **53**, 1276-1282. <https://doi.org/10.1038/s41588-021-00921-z>
- [12] Liu, C., Kanekiyo, T., Xu, H. and Bu, G. (2013) Apolipoprotein E and Alzheimer Disease: Risk, Mechanisms and Therapy. *Nature Reviews Neurology*, **9**, 106-118. <https://doi.org/10.1038/nrneurol.2012.263>
- [13] Strittmatter, W.J., Saunders, A.M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G.S., *et al.* (1993) Apolipoprotein E: High-Avidity Binding to Beta-Amyloid and Increased Frequency of Type 4 Allele in Late-Onset Familial Alzheimer Disease. *Proceedings of the National Academy of Sciences*, **90**, 1977-1981. <https://doi.org/10.1073/pnas.90.5.1977>
- [14] Gharbi-Meliani, A., Dugravot, A., Sabia, S., Regy, M., Fayosse, A., Schnitzler, A., *et al.* (2021) The Association of APOE E4 with Cognitive Function over the Adult Life Course and Incidence of Dementia: 20 Years Follow-Up of the Whitehall II Study. *Alzheimer's Research & Therapy*, **13**, Article No. 5. <https://doi.org/10.1186/s13195-020-00740-0>
- [15] Olichney, J.M., Sabbagh, M.N., Hofstetter, C.R., Galasko, D., Grundman, M.,

- Katzman, R., *et al.* (1997) The Impact of Apolipoprotein E4 on Cause of Death in Alzheimer's Disease. *Neurology*, **49**, 76-81. <https://doi.org/10.1212/WNL.49.1.76>
- [16] Sando, S.B., Melquist, S., Cannon, A., Hutton, M.L., Sletvold, O., Saltvedt, I., *et al.* (2008) APOE E4 Lowers Age at Onset and Is a High Risk Factor for Alzheimer's Disease; a Case Control Study from Central Norway. *BMC Neurology*, **8**, Article No. 9. <https://doi.org/10.1186/1471-2377-8-9>
- [17] Fleisher, A.S., Chen, K., Liu, X., Ayutyanont, N., Roontiva, A., Thiyyagura, P., *et al.* (2013) Apolipoprotein E E4 and Age Effects on Florbetapir Positron Emission Tomography in Healthy Aging and Alzheimer Disease. *Neurobiology of Aging*, **34**, 1-12. <https://doi.org/10.1016/j.neurobiolaging.2012.04.017>
- [18] Gonneaud, J., Arenaza-Urquijo, E.M., Fouquet, M., Perrotin, A., Fradin, S., de La Sayette, V., *et al.* (2016) Relative Effect of APOE E4 on Neuroimaging Biomarker Changes across the Lifespan. *Neurology*, **87**, 1696-1703. <https://doi.org/10.1212/WNL.0000000000003234>
- [19] Kantarci, K., Lowe, V., Przybelski, S.A., Weigand, S.D., Senjem, M.L., Ivnik, R.J., *et al.* (2012) APOE Modifies the Association between A β Load and Cognition in Cognitively Normal Older Adults. *Neurology*, **78**, 232-240. <https://doi.org/10.1212/WNL.0b013e31824365ab>
- [20] Kok, E., Haikonen, S., Luoto, T., Huhtala, H., Goebeler, S., Haapasalo, H., *et al.* (2009) Apolipoprotein E-Dependent Accumulation of Alzheimer Disease-Related Lesions Begins in Middle Age. *Annals of Neurology*, **65**, 650-657. <https://doi.org/10.1002/ana.21696>
- [21] Polvikoski, T., Sulkava, R., Haltia, M., Kainulainen, K., Vuorio, A., Verkkoniemi, A., *et al.* (1995) Apolipoprotein E, Dementia, and Cortical Deposition of B-Amyloid Protein. *New England Journal of Medicine*, **333**, 1242-1248. <https://doi.org/10.1056/NEJM199511093331902>
- [22] Verghese, P.B., Castellano, J.M., Garai, K., Wang, Y., Jiang, H., Shah, A., *et al.* (2013) APOE Influences Amyloid-B ($\alpha\beta$) Clearance Despite Minimal APOE/ $\alpha\beta$ Association in Physiological Conditions. *Proceedings of the National Academy of Sciences*, **110**, E1809-E1816. <https://doi.org/10.1073/pnas.1220484110>
- [23] Wildsmith, K.R., Holley, M., Savage, J.C., Skerrett, R. and Landreth, G.E. (2013) Evidence for Impaired Amyloid B Clearance in Alzheimer's Disease. *Alzheimer's Research & Therapy*, **5**, Article No. 33. <https://doi.org/10.1186/alzrt187>
- [24] Koffie, R.M., Hashimoto, T., Tai, H., Kay, K.R., Serrano-Pozo, A., Joyner, D., *et al.* (2012) Apolipoprotein E4 Effects in Alzheimer's Disease Are Mediated by Synaptotoxic Oligomeric Amyloid- β . *Brain*, **135**, 2155-2168. <https://doi.org/10.1093/brain/aws127>
- [25] Stevens, D.A., Workman, C.I., Kuwabara, H., Butters, M.A., Savonenko, A., Nassery, N., *et al.* (2022) Regional Amyloid Correlates of Cognitive Performance in Ageing and Mild Cognitive Impairment. *Brain Communications*, **4**, fcac016. <https://doi.org/10.1093/braincomms/fcac016>
- [26] Zhang, H., Jiang, X., Ma, L., Wei, W., Li, Z., Chang, S., *et al.* (2022) Role of A β in Alzheimer's-Related Synaptic Dysfunction. *Frontiers in Cell and Developmental Biology*, **10**, Article 964075. <https://doi.org/10.3389/fcell.2022.964075>
- [27] Therriault, J., Benedet, A.L., Pascoal, T.A., Mathotaarachchi, S., Chamoun, M., Savard, M., *et al.* (2020) Association of Apolipoprotein E E4 with Medial Temporal Tau Independent of Amyloid- β . *JAMA Neurology*, **77**, 470-479. <https://doi.org/10.1001/jamaneurol.2019.4421>
- [28] Rawat, P., Sehar, U., Bisht, J., Selman, A., Culbersson, J. and Reddy, P.H. (2022) Phos-

- phorylated Tau in Alzheimer's Disease and Other Tauopathies. *International Journal of Molecular Sciences*, **23**, Article 12841. <https://doi.org/10.3390/ijms232112841>
- [29] Wang, C., Xiong, M., Gratuze, M., Bao, X., Shi, Y., Andhey, P.S., *et al.* (2021) Selective Removal of Astrocytic APOE4 Strongly Protects against Tau-Mediated Neurodegeneration and Decreases Synaptic Phagocytosis by Microglia. *Neuron*, **109**, 1657-1674.e7. <https://doi.org/10.1016/j.neuron.2021.03.024>
- [30] Fernández-Pérez, E.J., Gallegos, S., Armijo-Weingart, L., Araya, A., Riffo-Lepe, N.O., Cayuman, F., *et al.* (2020) Changes in Neuronal Excitability and Synaptic Transmission in Nucleus Accumbens in a Transgenic Alzheimer's Disease Mouse Model. *Scientific Reports*, **10**, Article No. 19606. <https://doi.org/10.1038/s41598-020-76456-w>
- [31] Foust, A.J., Yu, Y., Popovic, M., Zecevic, D. and McCormick, D.A. (2011) Somatic Membrane Potential and Kv1 Channels Control Spike Repolarization in Cortical Axon Collaterals and Presynaptic Boutons. *The Journal of Neuroscience*, **31**, 15490-15498. <https://doi.org/10.1523/JNEUROSCI.2752-11.2011>
- [32] Jan, L.Y. and Jan, Y.N. (2012) Voltage-Gated Potassium Channels and the Diversity of Electrical Signalling. *The Journal of Physiology*, **590**, 2591-2599. <https://doi.org/10.1113/jphysiol.2011.224212>
- [33] Paulhus, K. and Glasscock, E. (2023) Novel Genetic Variants Expand the Functional, Molecular, and Pathological Diversity of KCNA1 Channelopathy. *International Journal of Molecular Sciences*, **24**, Article 8826. <https://doi.org/10.3390/ijms24108826>
- [34] Li, S. and Selkoe, D.J. (2020) A Mechanistic Hypothesis for the Impairment of Synaptic Plasticity by Soluble A β Oligomers from Alzheimer's Brain. *Journal of Neurochemistry*, **154**, 583-597. <https://doi.org/10.1111/jnc.15007>
- [35] Talantova, M., Sanz-Blasco, S., Zhang, X., Xia, P., Akhtar, M.W., Okamoto, S., *et al.* (2013) A β Induces Astrocytic Glutamate Release, Extrasynaptic NMDA Receptor Activation, and Synaptic Loss. *Proceedings of the National Academy of Sciences*, **110**, E2518-E2527. <https://doi.org/10.1073/pnas.1313546110>
- [36] Wang, R. and Reddy, P.H. (2017) Role of Glutamate and NMDA Receptors in Alzheimer's Disease. *Journal of Alzheimer's Disease*, **57**, 1041-1048. <https://doi.org/10.3233/JAD-160763>
- [37] Consens, M.E., Chen, Y., Menon, V., Wang, Y., Schneider, J.A., De Jager, P.L., *et al.* (2022) Bulk and Single-Nucleus Transcriptomics Highlight Intra-Telencephalic and Somatostatin Neurons in Alzheimer's Disease. *Frontiers in Molecular Neuroscience*, **15**, Article 903175. <https://doi.org/10.3389/fnmol.2022.903175>
- [38] Joshi, A., Giorgi, F.M. and Sanna, P.P. (2024) Transcriptional Patterns in Stages of Alzheimer's Disease Are Cell-Type-Specific and Partially Converge with the Effects of Alcohol Use Disorder in Humans. *eNeuro*, **11**, ENEURO.0118-24.2024. <https://doi.org/10.1523/ENEURO.0118-24.2024>
- [39] Gabitto, M.I., Travaglini, K.J., Rachleff, V.M., Kaplan, E.S., Long, B., Ariza, J., *et al.* (2024) Integrated Multimodal Cell Atlas of Alzheimer's Disease. *Nature Neuroscience*, **27**, 2366-2383. <https://doi.org/10.1038/s41593-024-01774-5>
- [40] Kumar, S., Zomorodi, R., Ghazala, Z., Goodman, M.S., Blumberger, D.M., Cheam, A., *et al.* (2017) Extent of Dorsolateral Prefrontal Cortex Plasticity and Its Association with Working Memory in Patients with Alzheimer Disease. *JAMA Psychiatry*, **74**, 1266-1274. <https://doi.org/10.1001/jamapsychiatry.2017.3292>
- [41] Bakken, T.E., Jorstad, N.L., Hu, Q., Lake, B.B., Tian, W., Kalmbach, B.E., *et al.* (2021) Comparative Cellular Analysis of Motor Cortex in Human, Marmoset and Mouse. *Nature*, **598**, 111-119. <https://doi.org/10.1038/s41586-021-03465-8>
- [42] Saito, T., Iwata, N., Tsubuki, S., Takaki, Y., Takano, J., Huang, S., *et al.* (2005) Soma-

- tostatin Regulates Brain Amyloid B Peptide A β 42 through Modulation of Proteolytic Degradation. *Nature Medicine*, **11**, 434-439.
<https://doi.org/10.1038/nm1206>
- [43] Miller, J.A., Gouwens, N.W., Tasic, B., Collman, F., *et al.* (2020) Common Cell Type Nomenclature for the Mammalian Brain. *E Life*, **9**, e59928.
<https://doi.org/10.7554/eLife.59928>
- [44] Patiño, M., Lagos, W.N., Patne, N.S., Tasic, B., Zeng, H. and Callaway, E.M. (2022) Single-Cell Transcriptomic Classification of Rabies-Infected Cortical Neurons. *Proceedings of the National Academy of Sciences*, **119**, e2203677119.
<https://doi.org/10.1073/pnas.2203677119>
- [45] Zhang, M., Eichhorn, S.W., Zingg, B., Yao, Z., Cotter, K., Zeng, H., *et al.* (2021) Spatially Resolved Cell Atlas of the Mouse Primary Motor Cortex by Merfish. *Nature*, **598**, 137-143. <https://doi.org/10.1038/s41586-021-03705-x>
- [46] Colom-Cadena, M., Spires-Jones, T., Zetterberg, H., Blennow, K., Caggiano, A., DeKosky, S.T., *et al.* (2020) The Clinical Promise of Biomarkers of Synapse Damage or Loss in Alzheimer's Disease. *Alzheimer's Research & Therapy*, **12**, Article No. 21.
<https://doi.org/10.1186/s13195-020-00588-4>
- [47] Lauterborn, J.C., Scaduto, P., Cox, C.D., Schulmann, A., Lynch, G., Gall, C.M., *et al.* (2021) Increased Excitatory to Inhibitory Synaptic Ratio in Parietal Cortex Samples from Individuals with Alzheimer's Disease. *Nature Communications*, **12**, Article No. 2603. <https://doi.org/10.1038/s41467-021-22742-8>
- [48] Scaduto, P., Lauterborn, J.C., Cox, C.D., Fracassi, A., Zeppillo, T., Gutierrez, B.A., *et al.* (2022) Functional Excitatory to Inhibitory Synaptic Imbalance and Loss of Cognitive Performance in People with Alzheimer's Disease Neuropathologic Change. *Acta Neuropathologica*, **145**, 303-324. <https://doi.org/10.1007/s00401-022-02526-0>
- [49] Dutertre, S., Becker, C. and Betz, H. (2012) Inhibitory Glycine Receptors: An Update. *Journal of Biological Chemistry*, **287**, 40216-40223.
<https://doi.org/10.1074/jbc.R112.408229>
- [50] Lynch, J.W. (2004) Molecular Structure and Function of the Glycine Receptor Chloride Channel. *Physiological Reviews*, **84**, 1051-1095.
<https://doi.org/10.1152/physrev.00042.2003>
- [51] Armijo-Weingart, L., San Martin, L., Gallegos, S., Araya, A., Konar-Nie, M., Fernandez-Pérez, E., *et al.* (2024) Loss of Glycine Receptors in the Nucleus Accumbens and Ethanol Reward in an Alzheimer's Disease Mouse Model. *Progress in Neurobiology*, **237**, Article 102616. <https://doi.org/10.1016/j.pneurobio.2024.102616>
- [52] Goldberg, E.M., Clark, B.D., Zaghera, E., Nahmani, M., Erisir, A. and Rudy, B. (2008) K⁺ Channels at the Axon Initial Segment Dampen Near-Threshold Excitability of Neocortical Fast-Spiking Gabaergic Interneurons. *Neuron*, **58**, 387-400.
<https://doi.org/10.1016/j.neuron.2008.03.003>
- [53] Kole, M.H.P., Letzkus, J.J. and Stuart, G.J. (2007) Axon Initial Segment Kv1 Channels Control Axonal Action Potential Waveform and Synaptic Efficacy. *Neuron*, **55**, 633-647. <https://doi.org/10.1016/j.neuron.2007.07.031>
- [54] Pathak, D., Guan, D. and Foehring, R.C. (2016) Roles of Specific Kv Channel Types in Repolarization of the Action Potential in Genetically Identified Subclasses of Pyramidal Neurons in Mouse Neocortex. *Journal of Neurophysiology*, **115**, 2317-2329.
<https://doi.org/10.1152/jn.01028.2015>
- [55] Lanznaster, D., Mack, J.M., Coelho, V., Ganzella, M., Almeida, R.F., Dal-Cim, T., *et al.* (2016) Guanosine Prevents Anhedonic-Like Behavior and Impairment in Hippocampal Glutamate Transport Following Amyloid- β 1-40 Administration in Mice. *Mo-*

- ecular Neurobiology*, **54**, 5482-5496.
<https://doi.org/10.1007/s12035-016-0082-1>
- [56] Scimemi, A., Meabon, J.S., Woltjer, R.L., Sullivan, J.M., Diamond, J.S. and Cook, D.G. (2013) Amyloid- β 1-42 Slows Clearance of Synaptically Released Glutamate by Mislocalizing Astrocytic GLT-1. *The Journal of Neuroscience*, **33**, 5312-5318.
<https://doi.org/10.1523/JNEUROSCI.5274-12.2013>
- [57] Ribarič, S. (2023) Detecting Early Cognitive Decline in Alzheimer's Disease with Brain Synaptic Structural and Functional Evaluation. *Biomedicines*, **11**, Article 355.
<https://doi.org/10.3390/biomedicines11020355>
- [58] Dauth, S., Maoz, B.M., Sheehy, S.P., Hemphill, M.A., Murty, T., Macedonia, M.K., *et al.* (2017) Neurons Derived from Different Brain Regions Are Inherently Different *in Vitro*: A Novel Multiregional Brain-on-a-Chip. *Journal of Neurophysiology*, **117**, 1320-1341. <https://doi.org/10.1152/jn.00575.2016>
- [59] Jacobs, H.I.L., Van Boxtel, M.P.J., Jolles, J., Verhey, F.R.J. and Uylings, H.B.M. (2012) Parietal Cortex Matters in Alzheimer's Disease: An Overview of Structural, Functional and Metabolic Findings. *Neuroscience & Biobehavioral Reviews*, **36**, 297-309.
<https://doi.org/10.1016/j.neubiorev.2011.06.009>
- [60] Migliaccio, R. and Cacciamani, F. (2022) The Temporal Lobe in Typical and Atypical Alzheimer Disease. In: *Handbook of Clinical Neurology*, Elsevier, 449-466.
<https://doi.org/10.1016/B978-0-12-823493-8.00004-3>