Published in final edited form as:

Neurobiol Aging. 2022 January ; 109: 158–165. doi:10.1016/j.neurobiolaging.2021.09.020.

APOE, *TOMM40*, and Sex Interactions on Neural Network Connectivity

Tianqi Li[1,*], **Colleen Pappas**[1,*], **Scott T. Le**[1], **Qian Wang**[1], **Brandon S. Klinedinst**[1], **Brittany Larsen**[1], **Amy Pollpeter**[1], **Ling Yi Lee**[2], **Mike W. Lutz**[3], **William K. Gottschalk**[3], **Russell H. Swerdlow**[4], **Kwangsik Nho**[5], **Auriel A. Willette**[1,6,7,8,†]

[1]Department of Food Science and Human Nutrition, Iowa State University, Ames, IA, USA

[2]Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[3]Department of Neurology, Duke University, Durham, NC

[4]Department of Neurology, University of Kansas, Kansas City, KS

[5]Department of Radiology and Imaging Sciences, Indiana University, Indianapolis, IN, USA

[6]Department of Biomedical Sciences, Iowa State University, Ames, IA, USA

[7]Department of Psychology, Iowa State University, Ames, IA, USA

[8]Department of Neurology, University of Iowa, Iowa City, IA, USA

Abstract

The Apolipoprotein E ε4 (*APOE* ε4) haplotype is the strongest genetic risk factor for late-onset Alzheimer‟s disease (AD). The Translocase of Outer Mitochondrial Membrane-40 (*TOMM40*) gene maintains cellular bioenergetics, which is disrupted in AD. *TOMM40* rs2075650 (‘650) G vs. A carriage is consistently related to neural and cognitive outcomes, but it is unclear if and how it interacts with *APOE.* We examined 21 orthogonal neural networks among 8,222 middle-aged to aged participants in the UK Biobank cohort. ANOVA and multiple linear regression tested main effects and interactions with *APOE* and *TOMM40* ‘650 genotypes, and if age and sex acted as moderators. *APOE* ε4 was associated with less strength in multiple networks, while ‘650 G vs. A

[†]Send Correspondence to: Auriel A. Willette, 1109 HNSB, 2302 Osborn Drive, Ames, IA 50011-1078, Awillett@iastate.edu.
[*]Both authors contributed equally to this report.

Tianqi Li, Writing- Reviewing, Software, Formal analysis and Editing; Colleen Pappas, Writing- Reviewing, Software, Formal analysis and Editing; Scott T. Le, Methodology, Writing- Original draft preparation, Data Curation, Visualization; Qian Wang, Methodology, Data Curation, Software; Brandon S. Klinedinst, Methodology, Conceptualization; Brittany Larsen, Writing - Original Draft; Amy Pollpeter, Writing - Original Draft; Ling Yi Lee, Methodology; Mike W. Lutz, Conceptualization; William K. Gottschalk, Conceptualization; Russell H. Swerdlow, Methodology; Kwangsik Nho, Methodology; Auriel A. Willette, Resources, Validation, Supervision, Funding acquisition

Verification

This manuscript is original and has not been published previously nor under consideration for publication elsewhere. All authors approve this publication and will not publish this elsewhere in the same form without written consent of the copyright-holder. mmc1.docx

Disclosure statement

The authors have declared no conflict of interest.

carriage was related to more language comprehension network strength. In *APOE* ε4 carriers, ‘650 G-carriage led to less network strength with increasing age, while in non G-carriers this was only seen in women but not men. *TOMM40* may shift what happens to network activity in aging *APOE* ε4 carriers depending on sex.

Keywords

TOMM40; resting state fMRI; APOE; default mode network; aging

1. Introduction

The Apolipoprotein E ε4 (*APOE* ε4*)* haplotype is the strongest genetic risk factor for late-onset Alzheimer‟s disease (AD), a neurodegenerative disorder characterized by progressive cognitive impairment and reduced brain activity both at rest and during task performance (Agosta et al., 2012; Corder et al., 1993; Farrer et al., 1997; McKenna, Koo, Killiany, & Initiative, 2016). Resting state functional magnetic resonance imaging (rsfMRI) is used to examine spontaneous changes over time in the amount of deoxygenated vs. oxygenated blood used to meet metabolic demand, a proxy for neural activity at baseline with no task (Ma et al., 2016). These spontaneous fluctuations are highly correlated within and across certain brain regions, resulting in consistent neural networks (Damoiseaux et al., 2006). Less neural network strength (i.e., functional connectivity or coupling) distinguishes patients with AD from cognitively unimpaired controls, and adults with mild cognitive impairment (MCI) who later convert to AD from those who remain stable (Binnewijzend et al., 2012; Sorg et al., 2007). Further, older unimpaired adults with *APOE* ε4 show less neural connectivity in the absence of amyloid deposition (Sheline et al., 2010). There are also some studies focusing on the association and interaction between APOE / TOMM40 and biomarkers (amyloid, tau or brain microstructure) (Siddarth et al., 2018; Tang et al., 2020), and the interaction between amyloid and APOE would be seen as targets of AD‟s prevention and/or treatment (Serrano-Pozo, Das, & Hyman, 2021; Wisniewski & Drummond, 2020). However, fMRI network activity has been used for detecting early AD-related cognitive impairment (Greicius, Srivastava, Reiss, & Menon, 2004; Z. Liu et al., 2012; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005) because it is sensitive and cheap (de Vos et al., 2018; Teipel et al., 2017).

The most common network examined is the Default Mode Network (DMN), which is vulnerable to AD (Buckner et al., 2009). This network robustly shows progressively less activity in adults who are at-risk or have MCI or AD. DMN consists of bilateral angular gyri, precuneus, and posterior cingulate cortex in the parietal lobe; anterior cingulate and medial prefrontal cortices in the frontal lobe; hippocampus; and thalamus (Binnewijzend et al., 2012). All of these areas show less glucose metabolism across the AD continuum. Yet, many other networks exist that regulate executive function, emotion regulation, memory recognition, association, and other behaviors or internal processes relevant to AD. Thus, we explored a comprehensive set of 21 neural networks determined in the UK Biobank (Alfaro-Almagro et al., 2018; Sudlow et al., 2015), a robust sample utilizing tens of thousands of scans.

Likewise, in genomics the *APOE* ε4 haplotype receives the majority of attention in AD, despite the other two *APOE* haplogroups. Specifically, it is unclear how the protective *APOE* ε2 allele (Corder et al., 1994) and "neutral risk" ε3 allele differ with regard to activity in these non-DMN networks, particularly in the context of other AD risk factors such as age and sex. Most especially, it is worthwhile to consider that genes surrounding the *APOE* gene on Chromosome 19 may also be relevant to detecting early hypoactivation in these networks. For example, Kulminski and colleagues discovered that three single nucleotide polymorphisms (SNPs) found on the APOE, TOMM40, and APOC1 genes work in concert to increase the risk of AD (Kulminski, Philipp, Loika, He, & Culminskaya, 2020). While several of these genes are in moderate linkage disequilibrium with *APOE*, at-risk genotypes may nonetheless impact neural network function. This would be critically important for early detection of participants who will eventually go on to develop AD.

In particular, Translocase of Outer Mitochondrial Membrane 40kD (*TOMM40*) is a nuclear-encoded gene that facilitates the import of nuclear encoded mitochondrial proteins, a process critical for cellular bioenergetics (Humphries et al., 2005). Many studies have shown that a G vs. A SNP on rs2075650 ('650) increases the risk for normal cognitive decline and also AD (Bagnoli et al., 2013; Omoumi et al., 2014; Valant et al., 2012). Other TOMM40 genotypes suggest that the '650 variant may also be related to neural network activity. For example, Evidence of rsfMRI characteristics suggested that the TOMM40 rs157581 SNP polymorphism could be associated with spontaneous regional brain activity (X. Liu et al., 2014). Specifically, TOMM40 rs157581-G AD carriers would have some brain functional connectivity decreased, and in their in the bilateral temporal, the low-frequency fluctuation amplitude also reduced (Xiao et al., 2019).

It is still open to debate whether these associations merely reflect LD with *APOE* (Davies et al., 2014; Yu et al., 2007). These studies only covaried the number of *APOE* ε4 alleles, however, and so a more careful consideration of the 3 *APOE* haplogroups and a larger sample may unravel the association with neural network strength. *APOE* stratification may also uncover synergistic effects with *TOMM40*. For example, it may be that *APOE* ε4 shows independent relationships itself, in conjunction with *TOMM40* '650, or possibly both depending on the phenotype. It may be easier to disentangle such effects using neural networks sensitive to AD vs. normal aging, rather than cognition or other biomarkers that appear much later in the disease process.

Accordingly, using genetic and rsfMRI data from the UK Biobank cohort, we tested the following associations on neural network strength at rest: 1) the main effects of the *APOE* haplotypes and interactions with sex and age; 2) the main effects of *TOMM40* '650 polymorphism and interactions with sex and age, among all participants; and 3) *TOMM40* '650 polymorphism main effects and interactions with sex and age stratified by *APOE*. This study will clarify how *APOE* and *TOMM40* risk variation influences early neural markers of AD, which in turn could improve precision medicine for disease treatment.

2. Methods

2.1. Cohort and Participants

The UK Biobank cohort includes a half million participants, aged 40 to 70 years at baseline recruitment, from 22 assessment centers located in the United Kingdom (Sudlow et al., 2015). There was a uniform lag for all participants between enrollment and measurement. The current study examined a sub-cohort of 8,222 participants with genomics, MRI, and demographics data. Participants completed informed consent prior to baseline examination. The cohort used for the current analyses is strictly British Europeans, as outlined by Bycroft and colleagues (Bycroft et al., 2018), due to racial and ethnic differences observed for the APOE haplotypes (Farrer et al., 1997). Participants with central nervous system disorders, cerebrovascular diseases, and any of the dementias were also excluded from the sample (see Supplementary Figure 1).

2.2. Genotyping

For *TOMM40*, genotype data for the SNP '650 were extracted for analyses using PLINK version 1.90 (https://www.cog-genomics.org/plink/1.9/). *TOMM40* '650 status was coded as those who were non-G carriers (AA homozygotes) versus G-carriers (GA and GG). *TOMM40* '650 was in the Hardy-Weinberg equilibrium (HWE) ($p = 0.6976$), indicating that frequency counts for these genotypes were in line with the general population. For *APOE* haplotype, a similar process was used for SNPs rs429358 and rs7412. Participants were categorized as having ε2, ε3, or ε4 isoforms. Participants classified as *APOE* ε2/ε4 were excluded from analyses. Linkage disequilibrium was also tested between rs2075650 and the APOE SNPs rs429358(R^2=.546) and rs7412 (R^2=.012).

2.3. Resting State fMRI – Acquisition and Processing

Participants were scanned at one of three sites in Reading, Newcastle, or Manchester on a Siemens Skyra 3T unit with a 32-channel RF receiver head coil (Siemens Medical Solutions, Erlangen, Germany) (Miller et al., 2016). Baseline MRI visits began in 2014 and longitudinal data collection is ongoing (Alfaro-Almagro et al., 2018). Participants were instructed to simply focus on a crosshair with eyes open and not think about anything specifically. Scan duration was 6 minutes and 10 seconds, to acquire 490 images with the following acquisition parameters: TR = 735*ms*; TE = 39*ms*; 2.4 × 2.4 × 2.4mm voxel resolution; 88 × 88 × 64 matrix, multiband factor = 8, in-plane acceleration factor = 1, flip angle 52°. Preprocessing and quality control measures are described in UK Biobank white papers (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf). Briefly, using FSL tools, the 4D dataset was motion-corrected, grand-mean intensity normalized, high-pass temporal filtered (with sigma = 50.0s), and EPI and GDC unwarped and denoised (using ICA+FIX processing). Group Principal Component Analysis and Independent Component Analysis through FMRIB's MELODIC were then used to derive 21 spatially orthogonal, non-noise, distinctive Independent Components (ICs) that represent resting neural networks (Kapogiannis, Reiter, Willette, & Mattson, 2013). Each participant has a Z-score for a given IC, representing the degree of activation relative to the group mean. An expert (AAW) then viewed the activation maps and described the neural networks (see Supplementary Table 1).

2.4. Covariates

For main effect and interaction analyses of *APOE* or *TOMM40* '650 genotype, covariates included factors that may protect or weaken neural network strength such as sex, age at recruitment, social class, education level, and family history of AD. Social class was categorically derived from gross annual household income between 2008 and 2014 as "lower class" (<£18,000), "middle class" (£18,000-£51,999), and "upper class" (£52 000 to > £100,000). Education level was categorized as: college or higher qualifications (3); post-secondary or vocational (2); secondary (1); and none of the above (0).

2.5. Statistical Analysis

Multiple linear regression equations were modeled using R, version 3.6.1 (R Foundation for Statistical Programming, Vienna, Austria) and SPSS 26 (SPSS Inc., Chicago, IL, USA). Initial analyses tested the main effect of *APOE* haplotype (ε2, ε3, ε4) on all 21 neural networks, followed by interactions with age in years and sex. The ε3 allele group was set as the reference group. ANCOVA was used in follow-up tests to examine differences among *APOE* groups. Next, we examined the main effect of *TOMM40* '650 G carriage and interactions with age in years and sex. *APOE* was added to the *TOMM40* models as a covariate and recoded as a dichotomous variable based on whether the participant carried ε4 or not. These analyses were conducted across all participants.

Finally, *TOMM40* '650 G carriage analyses were repeated, but now separately in each of the *APOE* haplogroups (ε2 = ε2/ ε2, ε2/ ε3; ε3= ε3/ ε3; ε4= ε3/ ε4, ε4/ ε4) with regard for age and sex. As we and others show, there is moderate genetic linkage disequilibrium between *TOMM40* '650 and one of the major *APOE* SNPs, rs429358, but not *APOE* rs7412 (Corder et al., 1993; Deelen et al., 2011; Farrer et al., 1997; Potkin et al., 2009). However, to date, most studies of *TOMM40* have covaried the number of *APOE* ε4 alleles, which may overlook effects of the '650 SNP. To examine if independent (Elias-Sonnenschein et al., 2013; Omoumi et al., 2014), dependent (Soyal et al., 2020), or synergistic (Ferencz, Karlsson, & Kalpouzos, 2012; Moon et al., 2015) gene x gene effects manifest, it is more appropriate to test TOMM40 '650 when stratified by *APOE* ε2, ε3, or ε4 carriage.

ANCOVA was used in follow-up tests to examine differences between '650 G vs. non-G carriers. To address Power, sensitivity analyses were conducted for each set of studies using GPower 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). Significant effects (ps<.05) were corrected for multiple comparisons using the Scheffe method because the groups have unequal sample sizes. Family-wise Alpha was set at p=0.05. Estimated marginal means were calculated using *emmeans* (Lenth, Singmann, Love, Buerkner, & Herve, 2020). The figures were produced using *ggplot2* (Wickham, 2019) and SPSS 26.

2.6. Corrections for Multiple Comparisons

A total of 21 neural networks were examined, requiring multiple comparison correction to avoid false positives. For each predictor of interest (i.e., APOE haplotype, TOMM40 genotype), a series of Type I error correction techniques were utilized. First, a multivariate analysis of covariance (MANCOVA) omnibus test was conducted. If the omnibus was significant, follow-up models were completed with a family-wise error rate of .05 (Hummel

& Sligo, 1971). If the omnibus MANCOVA was not significant (p>.05), a Holm-Bonferroni correction was applied as described in previous work (Willette, Modanlo, Kapogiannis, & Alzheimer's Disease Neuroimaging, 2015).

3. Results

3.1. Descriptive Statistics

The sample included 8,222 participants. Demographic and clinical data are presented in Table 1. The average age of participants was 55 years (SD = 7.47) and approximately 52% were women. Most participants had a college or higher qualification. Slightly more than half participants reported incomes of between £18,000 - £51,999 (i.e., "middle class").

3.2. *APOE* Only - Main Effects and Interactions

In contrast with ε3 carriers, ε4 carriers as expected had significant less network strength in executive function, memory retrieval, memory storage, motor planning, posterior default mode, and language processing networks (see Figure 1 and Table 2). Conversely, ε2 carriers when compared to ε3 carriers had more neural activity only in a network composed of posterior DMN. No age, sex, or exploratory age by sex interactions were observed with *APOE* ε4 carriers for any resting state network.

3.3. *TOMM40* '650 Only - Main Effects and Interactions

For main effects, '650 G-allele carriage was associated with more network strength only in an auditory and language comprehension network (see Table 3; Figure 2, left panel). Those *APOE* ε4 vs. non-ε4 carriers had less activity in this auditory/language network and posterior DMN (Figure 2, right panel). Based on a '650 Carriage by Sex interaction for the auditory/language network (p=.0453, G carrier vs. non-carrier), G-carrier men had more network strength ($M_{diff=}$.072, SE=.023, p=.020), but G-carrier women did not (M_{diff}=.007, SE=.022, p>0.10). No other two-way or exploratory 3-way interactions were present.

3.4. *TOMM40* '650 Stratified by APOE Haplotype – Main Effects and Interactions

There were no main effects or 2-way interactions with sex or age for any *APOE* haplogroup. Among *APOE* ε4 carriers, every neural network showed robust 3-way interactions between *TOMM40* '650 G carriage, sex, and age (all p<.001) (Table 4). Figure 3 illustrates an example with DMN, where the relationship between age in years and network strength is modified by sex and *TOMM40* '650. For *TOMM40* '650 non-G carriers, per year of age, older women but not men showed less network strength. By contrast, among both sexes identically, *TOMM40* '650 G carriers showed less network strength per year of age. There were no 3-way *TOMM40* '650 x age x sex interactions present among *APOE* ε4 non-carriers.

4. Discussion

This study examined main effects and interactions among different *APOE* or *TOMM40* '650 genotypes alone, and analyzed *TOMM40* when stratified by *APOE* ε2, ε3, or ε4. As expected, *APOE* ε itself was related to less activity in several resting state networks relevant

to AD, including memory consolidation, central executive function, and the posterior portion of default mode network (Sheline et al., 2010). While normative aging affects the whole brain, the posterior DMN is the most sensitive network in patients with AD (Klaassens et al., 2017). Similar work has established the role of *APOE* ε4 in worse episodic memory(Kerchner et al., 2014). Although lower executive function was observed in non-*APOE ε4* carriers(Wolk, Dickerson, & Initiative, 2010), the ε4 carriers demonstrated more rapid executive function decline in community-dwelling older adults (Reas et al., 2019). Cortical auditory processing has also been deemed a relevant biomarker for preclinical AD, but not with *APOE* ε4 (Tuwaig et al., 2017).

To our knowledge, this is the first study to examine independent, dependent, and synergistic associations between *TOMM40* '650, *APOE*, and resting state neural networks. *TOMM40* '650 G carriage by itself, after covarying *APOE*, appears to specifically influence auditory and language comprehension network processing. These processes encompass the Wernicke‟s area, prefrontal and subcortical brain regions, demonstrating the large magnitude of this network (Tomasi & Volkow, 2012). Aside from memory, progressive language impairment can be a feature of AD (Verma & Howard, 2012). Unexpectedly, the '650 G risk allele was related to more network strength, specifically for men but not women. Another UK Biobank Study also observed that men had more functional connectivity between unimodal sensory and motor cortices (Ritchie et al., 2018). Cavedo et al. suggested that compared with women, older adult men could have lower resting-state functional connectivity in the default mode network (Cavedo et al., 2018). Therefore, men with the high-risk G-allele could be showing increased activity as some sort of compensatory strategy specific to language processing. While we did observe sex effects across all neural networks, sex alone is not enough to distinguish individual brain resting state patterns (Weis et al., 2020).

When examining *TOMM40* '650 associations stratified by *APOE* genotype, age and sex appeared to uncover key gene x gene interactions for the *APOE* ε4 risk group. While it has been well documented that older age drives reduced neural network strength (Buckner et al., 2005), this did not hold true for men without the '650 G allele in our study. It is unclear why only men may be affected. Nonetheless, modulation of *APOE* ε4 by *TOMM40* '650 may help to elucidate why *APOE* ε4 carriage shows phenotypic variation among middle-aged to early aged adults.

There are notable limitations to address. Since our sample was comprised of British Europeans, our results may not be generalized to other ethnic/racial groups. While *TOMM40* '650 polymorphisms contribute similarly to AD in White and Asian populations (Huang et al., 2016), future analyses with more diverse cohorts will be needed to examine modulation by race or ethnicity. While follow-up MRI scans are being conducted by UK Biobank, existing data are cross-sectional and correlational. Thus, causality cannot be implied. Despite the limitations outlined, there are strengths to note. We used a large sample to determine genetic effects on resting state neural networks, which is an early marker of AD pathology. A total of 21 networks were examined rather than focusing solely on the DMN. Finally, we tested interactions with age and sex, which provided further insight about how TOMM40 '650 G-carrier status impacts men and women differently.

Taken together, our study results indicated that TOMM40 rs'650 genotype impacts neural network strength among middle-aged to older adults. The current study may reflect that more neural networks are vulnerable to *APOE* ε4 than the *TOMM40* polymorphism, but that '650 G-carriage nonetheless can strongly influence how sex and age are related to network strength. Assessment of functional neural network strength at multiple time points may uncover changes with brain atrophy and cognitive decline. Novel AD genetic risk factors without LD to *APOE* should also be examined with resting state network strength as an outcome, as aforementioned studies besides the current study have demonstrated its utility (Binnewijzend et al., 2012; Sorg et al., 2007).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research has been conducted using the UK Biobank Resource under Application Number 25057. This work was supported by Iowa State University, National Institutes of Health (NIH) R00 AG047282, and Alzheimer"s Association Research Grant to Promote Diversity (AARG-D)-17–529552. Funding sources had no influence on the development or conduct of this report.

References

Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni GB, & Filippi M. (2012). Resting state fMRI in Alzheimer's disease: Beyond the default mode network. Neurobiology of Aging, 33, 1564–1578. doi:10.1016/j.neurobiolaging.2011.06.007 [PubMed: 21813210]

Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, … Smith SM (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage, 166, 400–424. doi:10.1016/j.neuroimage.2017.10.034 [PubMed: 29079522]

Bagnoli S, Piaceri I, Tedde A, Bessi V, Bracco L, Sorbi S, & Nacmias B. (2013). Tomm40 polymorphisms in Italian Alzheimer's disease and frontotemporal dementia patients. Neurological Sciences, 34, 995–998. doi:10.1007/s10072-013-1425-6 [PubMed: 23546992]

Binnewijzend MAA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, … Barkhof F. (2012). Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiology of Aging, 33, 2018–2028. doi:10.1016/j.neurobiolaging.2011.07.003 [PubMed: 21862179]

Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, … Johnson KA (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. Journal of Neuroscience, 29, 1860–1873. doi:10.1523/JNEUROSCI.5062-08.2009 [PubMed: 19211893]

Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, … Mintun MA (2005). Molecular, structural, and functional characterization of Alzheimer's disease: Evidence for a relationship between default activity, amyloid, and memory. Journal of Neuroscience, 25, 7709–7717. doi:10.1523/JNEUROSCI.2177-05.2005 [PubMed: 16120771]

Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, … Marchini J. (2018). The UK Biobank resource with deep phenotyping and genomic data. Nature, 562, 203–209. doi:10.1038/s41586-018-0579-z [PubMed: 30305743]

Cavedo E, Chiesa PA, Houot M, Ferretti MT, Grothe MJ, Teipel SJ, … Hampel H. (2018). Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in cognitively normal older adults with subjective memory complaints. Alzheimer's and Dementia, 14, 1204–1215. doi:10.1016/j.jalz.2018.05.014

Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, … Pericak-Vance MA (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature Genetics, 7, 180–184. doi:10.1038/ng0694-180 [PubMed: 7920638]

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, … Pericak-Vance MA (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 261, 921–923. doi:10.1126/science.8346443 [PubMed: 8346443]

Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM, & Beckmann CF (2006). Consistent resting-state networks across healthy subjects. Proceedings of the National Academy of Sciences of the United States of America, 103, 13848–13853. doi:10.1073/pnas.0601417103 [PubMed: 16945915]

Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, Liewald DC, … Deary IJ (2014). A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. Molecular Psychiatry, 19, 76–87. doi:10.1038/mp.2012.159 [PubMed: 23207651]

de Vos F, Koini M, Schouten TM, Seiler S, van der Grond J, Lechner A, … Rombouts S. (2018). A comprehensive analysis of resting state fMRI measures to classify individual patients with Alzheimer's disease. Neuroimage, 167, 62–72. doi:10.1016/j.neuroimage.2017.11.025 [PubMed: 29155080]

Deelen J, Beekman M, Uh HW, Helmer Q, Kuningas M, Christiansen L, … Slagboom PE (2011). Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. Aging Cell, 10, 686–698. doi:10.1111/j.1474-9726.2011.00705.x [PubMed: 21418511]

Elias-Sonnenschein LS, Helisalmi S, Natunen T, Hall A, Paajanen T, Herukka SK, … Hiltunen M. (2013). Genetic Loci Associated with Alzheimer's Disease and Cerebrospinal Fluid Biomarkers in a Finnish Case-Control Cohort. PLoS One, 8. doi:10.1371/journal.pone.0059676

Farrer LA, Cupples A, Haines JL, Hyman B, Kukull WA, Mayeux R, … van Duijn CM (1997). Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease. JAMA, 278, 1349. doi:10.1001/jama.1997.03550160069041 [PubMed: 9343467]

Faul F, Erdfelder E, Buchner A, & Lang A-G (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41, 1149–1160. doi:10.3758/BRM.41.4.1149 [PubMed: 19897823]

Ferencz B, Karlsson S, & Kalpouzos G. (2012). Promising genetic biomarkers of preclinical Alzheimer's disease: The influence of APOE and TOMM40 on brain integrity. International Journal of Alzheimer's Disease, 2012. doi:10.1155/2012/421452

Greicius MD, Srivastava G, Reiss AL, & Menon V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A, 101(13), 4637–4642. doi:10.1073/pnas.0308627101 [PubMed: 15070770]

Huang H, Zhao J, Xu B, Ma X, Dai Q, Li T, … Chen B. (2016). The TOMM40 gene rs2075650 polymorphism contributes to Alzheimer's disease in Caucasian, and Asian populations. Neuroscience Letters, 628, 142–146. doi:10.1016/j.neulet.2016.05.050 [PubMed: 27328316]

Hummel TJ, & Sligo JR (1971). Empirical comparison of univariate and multivariate analysis of variance procedures. Psychological Bulletin, 76(1), 49–57.

Humphries AD, Streimann IC, Stojanovski D, Johnston AJ, Yano M, Hoogenraad NJ, & Ryan MT (2005). Dissection of the mitochondrial import and assembly pathway for human Tom40. Journal of Biological Chemistry, 280, 11535–11543. doi:10.1074/jbc.M413816200

Kapogiannis D, Reiter DA, Willette AA, & Mattson MP (2013). Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. Neuroimage, 64, 112–119. doi:10.1016/j.neuroimage.2012.09.029 [PubMed: 23000786]

Kerchner GA, Berdnik D, Shen JC, Bernstein JD, Fenesy MC, Deutsch GK, … Rutt BK (2014). APOE e4 worsens hippocampal CA1 apical neuropil atrophy and episodic memory. Neurology, 82, 691–697. doi:10.1212/WNL.0000000000000154 [PubMed: 24453080]

Klaassens BL, van Gerven JMA, van der Grond J, de Vos F, Möller C, & Rombouts SARB (2017). Diminished posterior precuneus connectivity with the default mode network differentiates normal aging from Alzheimer's Disease. Frontiers in Aging Neuroscience, 9, 1–13. doi:10.3389/fnagi.2017.00097 [PubMed: 28174533]

Kulminski AM, Philipp I, Loika Y, He L, & Culminskaya I. (2020). Haplotype architecture of the Alzheimer's risk in the APOE region via co-skewness. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring, 12, 1–10. doi:10.1002/dad2.12129

Lenth R, Singmann H, Love J, Buerkner P, & Herve M. (2020). emmeans.

Liu X, Bai F, Yue C, Shi Y, Yu H, Luo B, & Zhang Z. (2014). The association between TOMM40 gene polymorphism and spontaneous brain activity in amnestic mild cognitive impairment. J Neurol, 261(8), 1499–1507. doi:10.1007/s00415-014-7368-x [PubMed: 24838536]

Liu Z, Zhang Y, Yan H, Bai L, Dai R, Wei W, … Tian J. (2012). Altered topological patterns of brain networks in mild cognitive impairment and Alzheimer's disease: a resting-state fMRI study. Psychiatry Res, 202(2), 118–125. doi:10.1016/j.pscychresns.2012.03.002 [PubMed: 22695315]

Ma Y, Shaik MA, Kozberg MG, Kim SH, Portes JP, Timerman D, & Hillman EMC (2016). Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons. Proceedings of the National Academy of Sciences of the United States of America, 113, E8463–E8471. doi:10.1073/pnas.1525369113 [PubMed: 27974609]

McKenna F, Koo BB, Killiany R, & Initiative, f. t. A. s. D. N. (2016). Comparison of ApoE-related brain connectivity differences in early MCI and normal aging populations: an fMRI study. Brain Imaging and Behavior, 10, 970–983. doi:10.1007/s11682-015-9451-z [PubMed: 26409470]

Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, … Smith SM (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nature Neuroscience, 19, 1523–1536. doi:10.1038/nn.4393 [PubMed: 27643430]

Moon SW, Dinov ID, Kim J, Zamanyan A, Hobel S, Thompson PM, & Toga AW (2015). Structural Neuroimaging Genetics Interactions in Alzheimer's Disease. Journal of Alzheimer's Disease, 48, 1051–1063. doi:10.3233/JAD-150335

Omoumi A, Fok A, Greenwood T, Sadovnick AD, Feldman HH, & Hsiung GYR (2014). Evaluation of late-onset Alzheimer disease genetic susceptibility risks in a Canadian population. Neurobiology of Aging, 35, 936.e935–936.e912. doi:10.1016/j.neurobiolaging.2013.09.025

Potkin SG, Guffanti G, Lakatos A, Turner JA, Kruggel F, Fallon JH, … Macciardi F. (2009). Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's Disease. PLoS One, 4. doi:10.1371/journal.pone.0006501

Reas ET, Laughlin GA, Bergstrom J, Kritz-Silverstein D, Barrett-Connor E, & McEvoy LK (2019). Effects of APOE on cognitive aging in community-dwelling older adults. Neuropsychology, 33, 406–416. doi:10.1037/neu0000501 [PubMed: 30730162]

Ritchie SJ, Cox SR, Shen X, Lombardo MV, Reus LM, Alloza C, … Deary IJ (2018). Sex differences in the adult human brain: Evidence from 5216 UK biobank participants. Cerebral Cortex, 28, 2959–2975. doi:10.1093/cercor/bhy109 [PubMed: 29771288]

Rombouts SA, Barkhof F, Goekoop R, Stam CJ, & Scheltens P. (2005). Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Hum Brain Mapp, 26(4), 231–239. doi:10.1002/hbm.20160 [PubMed: 15954139]

Serrano-Pozo A, Das S, & Hyman BT (2021). APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol, 20(1), 68–80. doi:10.1016/S1474-4422(20)30412-9 [PubMed: 33340485]

Sheline YI, Morris JC, Snyder AZ, Price JL, Yan Z, D'Angelo G, … Mintun MA (2010). APOE4 allele disrupts resting state fMRI connectivity in the absence of amyloid plaques or decreased CSF Aβ42. Journal of Neuroscience, 30, 17035–17040. doi:10.1523/JNEUROSCI.3987-10.2010 [PubMed: 21159973]

Siddarth P, Burggren AC, Merrill DA, Ercoli LM, Mahmood Z, Barrio JR, & Small GW (2018). Longer TOMM40 poly-T variants associated with higher FDDNP-PET medial temporal tau and amyloid binding. PLoS One, 13(12), e0208358. doi:10.1371/journal.pone.0208358 [PubMed: 30517207]

Sorg C, Riedl V, Mühlau M, Calhoun VD, Eichele T, Läer L, … Wohlschläger AM (2007). Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America, 104, 18760–18765. doi:10.1073/pnas.0708803104 [PubMed: 18003904]

Soyal SM, Kwik M, Kalev O, Lenz S, Zara G, Strasser P, … Weis S. (2020). A TOMM40/APOE allele encoding APOE-E3 predicts high likelihood of late-onset Alzheimer's disease in autopsy cases. Molecular Genetics and Genomic Medicine, 8, 1–13. doi:10.1002/mgg3.1317

Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, … Collins R. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLOS Medicine, 12, e1001779. doi:10.1371/journal.pmed.1001779 [PubMed: 25826379]

Tang ME, Blair JPM, Bager CL, Bay-Jensen AC, Henriksen K, Christiansen C, & Karsdal MA (2020). Matrix metalloproteinase-degraded type I collagen is associated with APOE/TOMM40 variants and preclinical dementia. Neurol Genet, 6(5), e508. doi:10.1212/NXG.0000000000000508 [PubMed: 33134509]

Teipel SJ, Wohlert A, Metzger C, Grimmer T, Sorg C, Ewers M, … Dyrba M. (2017). Multicenter stability of resting state fMRI in the detection of Alzheimer's disease and amnestic MCI. Neuroimage Clin, 14, 183–194. doi:10.1016/j.nicl.2017.01.018 [PubMed: 28180077]

Tomasi D, & Volkow ND (2012). Resting functional connectivity of language networks: Characterization and reproducibility. Molecular Psychiatry, 17, 841–854. doi:10.1038/mp.2011.177 [PubMed: 22212597]

Tuwaig M, Savard M, Jutras B, Poirier J, Collins DL, Rosa-Neto P, … Breitner JCS (2017). Deficit in Central Auditory Processing as a Biomarker of Pre-Clinical Alzheimer's Disease. Journal of Alzheimer's Disease, 60, 1589–1600. doi:10.3233/JAD-170545

Valant V, Keenan BT, Anderson CD, Shulman JM, Devan WJ, Ayres AM, … Biffi A. (2012). TOMM40 in Cerebral Amyloid Angiopathy Related Intracerebral Hemorrhage: Comparative Genetic Analysis with Alzheimer's Disease. Translational Stroke Research, 3, 102–112. doi:10.1007/s12975-012-0161-1 [PubMed: 24323865]

Verma M, & Howard RJ (2012). Semantic memory and language dysfunction in early Alzheimer's disease: A review. International Journal of Geriatric Psychiatry, 27, 1209–1217. doi:10.1002/gps.3766 [PubMed: 22298328]

Weis S, Patil KR, Hoffstaedter F, Nostro A, Yeo BTT, & Eickhoff SB (2020). Sex Classification by Resting State Brain Connectivity. Cerebral cortex (New York, N.Y. : 1991), 30, 824–835. doi:10.1093/cercor/bhz129

Wickham R. (2019). ggplot2: Elegant Graphics for Data Analysis.

Willette AA, Modanlo N, Kapogiannis D, & Alzheimer's Disease Neuroimaging I. (2015). Insulin resistance predicts medial temporal hypermetabolism in mild cognitive impairment conversion to Alzheimer disease. Diabetes, 64(6), 1933–1940. doi:10.2337/db14-1507 [PubMed: 25576061]

Wisniewski T, & Drummond E. (2020). APOE-amyloid interaction: Therapeutic targets. Neurobiol Dis, 138, 104784. doi:10.1016/j.nbd.2020.104784 [PubMed: 32027932]

Wolk DA, Dickerson BC, & Initiative, a. t. A. s. D. N. (2010). Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America, 107, 10256–10261. doi:10.1073/pnas.1001412107 [PubMed: 20479234]

Xiao X, Wei J, Zhang W, Jiao B, Liao X, Pan C, … Shen L. (2019). TOMM40 polymorphism is associated with resting-state functional MRI results in patients with Alzheimer's disease. Neuroreport, 30(16), 1068–1073. doi:10.1097/WNR.0000000000001297 [PubMed: 31568198]

Yu CE, Seltman H, Peskind ER, Galloway N, Zhou PX, Rosenthal E, … Schellenberg GD (2007). Comprehensive analysis of APOE and selected proximate markers for late-onset Alzheimer's disease: Patterns of linkage disequilibrium and disease/marker association. Genomics, 89, 655–665. doi:10.1016/j.ygeno.2007.02.002 [PubMed: 17434289]

Highlights

- Sex modifies the relationship between *TOMM40* ‘650 and network strength
- interactions between ‘650, sex, and age were in APOE4 carriers‟ neural networks
- Older ‘650 G and *APOE4* carriers showed less neural network connectivity

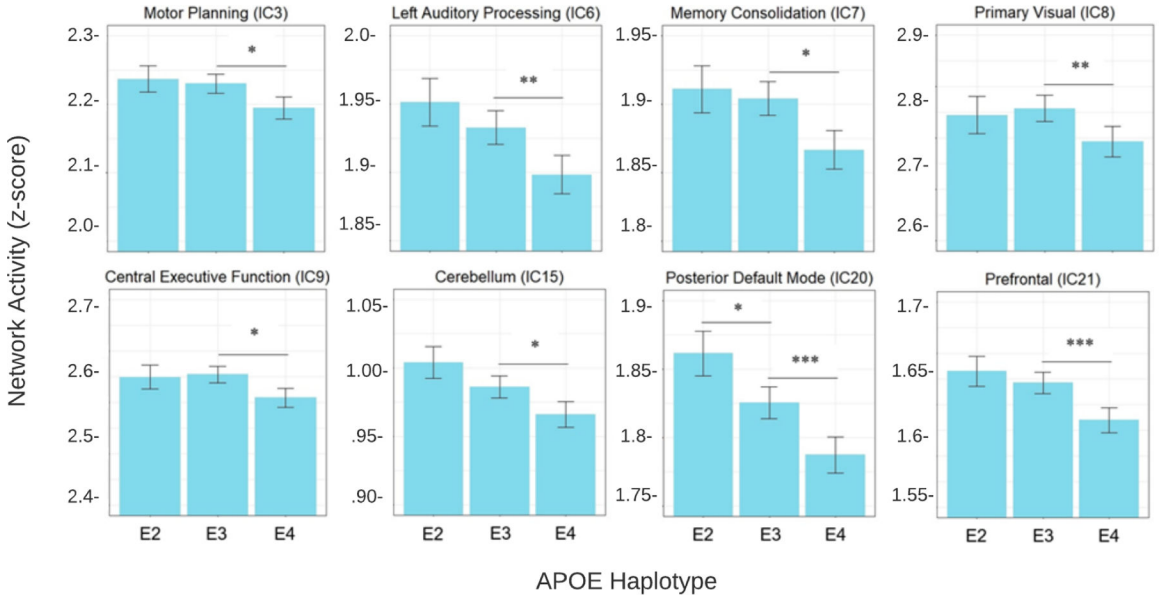

Figure 1.

Refer to Supplementary Table 1 for detailed descriptions of networks. Networks are inferred from Independent Components, abbreviated as ICs, that were derived using Independent Component Analysis on resting state data. For brevity, only the shown ICs had significant differences between the ε3 reference group and ε4 carriers. **,***=p<.01, .001.

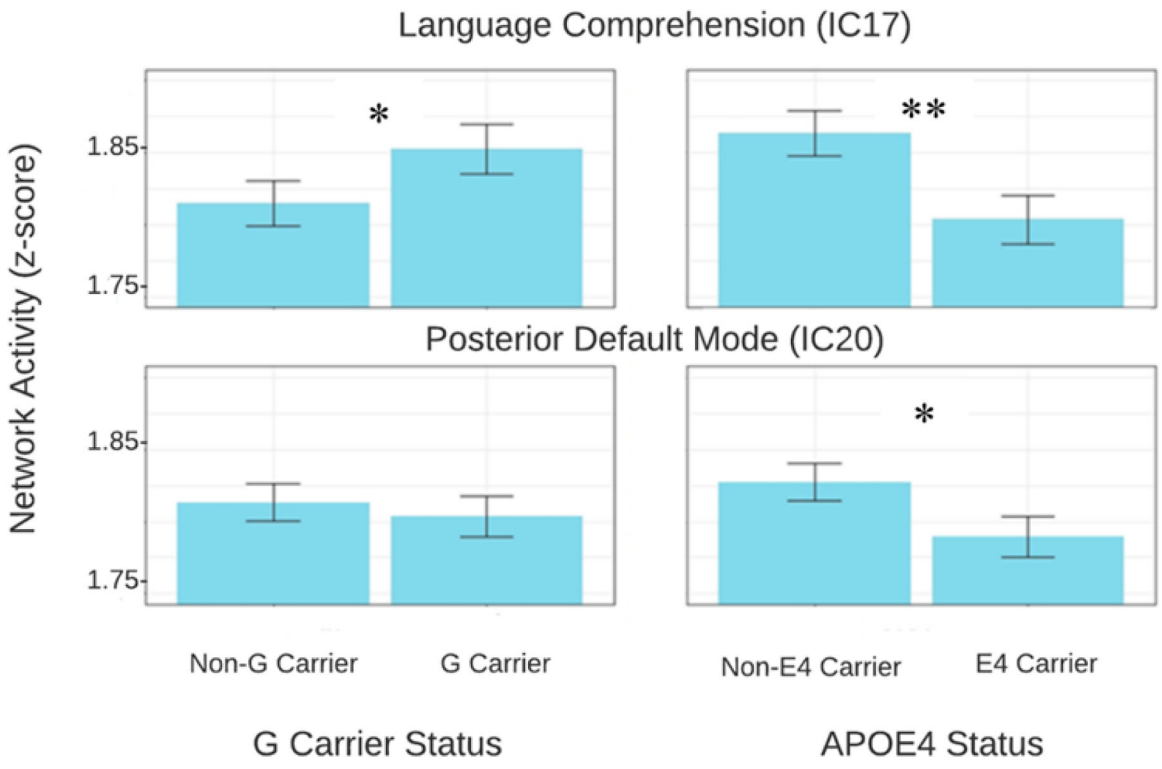

Figure 2.

Refer to Supplementary Table 1 for detailed descriptions of the Language/Auditory and Default Mode Networks. Networks are inferred from Independent Components, abbreviated as ICs, that were derived using Independent Component Analysis on resting state data. For brevity, only the shown ICs had significant differences between ε4 carriers and non-ε4 carriers. *,**=p<.05, .01.

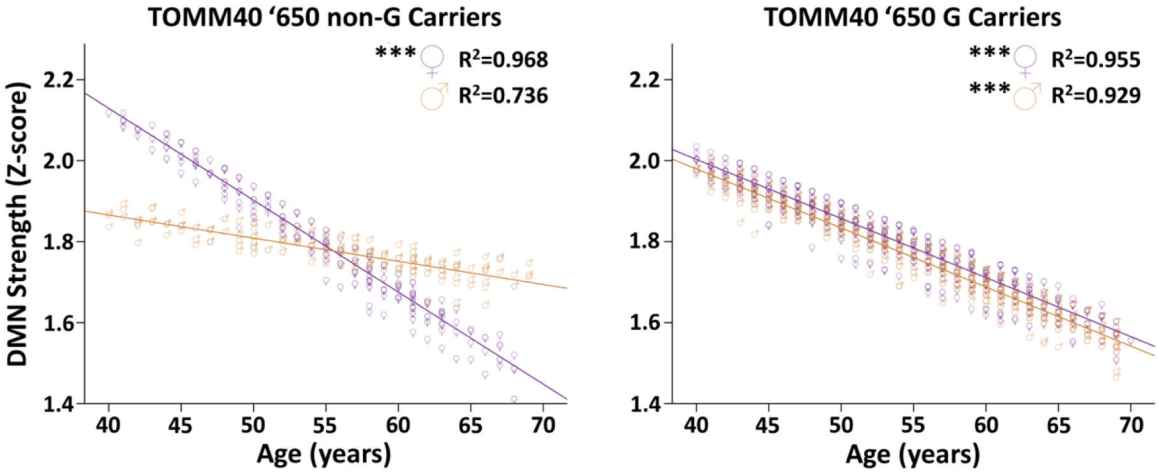

Figure 3.

Purple and gold-yellow symbols respectively represent datapoints for women and men. ***=p<.001.

Table 1.

Participant Characteristics and Data Summary

Age at recruitment, years	55.12 ± 7.47
Sex, no (%)	
Female	4269 (51.9)
Male	3953 (48.1)
Education, no (%)	
College or higher qualifications	5338 (64.9)
Post-secondary or vocational	1526 (18.6)
Secondary	943 (11.5)
None of the above	415 (5.1)
Social Class, no (%)	
Lower	3644 (44.3)
Middle	4264 (51.9)
Upper	314 (3.8)
Positive Family History of AD, no. (%)	2043 (24.8)
TOMM40 G carrier, no. (%)	2356 (25.4)
APOE ε4 carrier, no. (%)	2135 (26.0)
APOE ε4 also TOMM40 G carrier, no. (%)	1679 (78.6)

Table 2.

APOE Genotype Main Effects and Interactions on Neural Network Strength

IC	Neural Network	*APOE* ε2 Group			*APOE* ε4 Group		
		β	SE	p-value	β	SE	p-value
1	Default Mode	0.012	0.0189	.285	−0.026	0.015	.018
2	“Where and “What” Pathways	−0.007	0.0219	.538	−0.015	0.017	.190
3	Motor Planning	0.004	0.0169	.687	**−0.030**	**0.013**	**.007**
4	Extrastriate Visual	−0.010	0.0207	.377	−0.020	0.016	.072
5	Left Executive Function	0.007	0.0165	.544	−0.024	0.013	.031
6	Auditory and Speech	0.014	0.0152	.221	**−0.032**	**0.012**	**.004**
7	Memory Consolidation	0.005	0.0149	.648	**−0.036**	**0.012**	**.001**
8	Primary Visual	−0.005	0.0318	.681	**−0.029**	**0.025**	**.009**
9	Central Executive Function	−0.003	0.0198	.803	**−0.032**	**0.015**	**.004**
10	Affect Processing	0.005	0.0197	.626	−0.015	0.015	.176
11	Motor Execution	0.012	0.0144	.283	−0.013	0.011	.230
12	Sensorimotor	0.016	0.0158	.146	−0.022	0.012	.051
13	Right Executive Function	−0.004	0.0124	.713	−0.024	0.010	.031
14	Fronto-Cingular	0.022	0.0100	.041	−0.004	0.008	.732
15	Cerebellum	0.019	0.0101	.078	**−0.028**	**0.008**	**.011**
16	Frontopolar	0.020	0.0144	.065	−0.011	0.011	.305
17	Auditory/Language	0.015	0.0170	.182	−0.024	0.013	.029
18	Cortico-Striatal	0.009	0.0094	.384	−0.016	0.007	.142
19	Primary Visual	−0.006	0.0253	.568	−0.027	0.020	.015
20	Posterior Default Mode	**0.028**	**0.0142**	.011	**−0.038**	**0.011**	**<.001**
21	Prefrontal + “What” Pathway	0.010	0.0130	.382	**−0.040**	**0.010**	**<.001**

See Supplementary Table 1 for descriptions of all 21 independent neural networks. *APOE* ε3 is the reference group for separate comparisons between ε2 or ε4. . Estimates that survived multiple comparisons correction are indicated by bold text. The model consisted of *APOE* Groups + Age + Sex + Education + Social Class + Family History AD. Age and sex interactions were not present in separate models. .

Table 3.

Main Effects and Interactions of *TOMM40* '650 G Carriage on Neural Network Strength

		Model I			Model II		
		'650 G Carriage Only			G Carriage * Sex		
IC	Neural Network	β	SE	p-value	β	SE	p-value
1	Default Mode	0.005	0.021	.724	−0.028	0.029	0.248
2	"Where and "What" Pathways	−0.011	0.024	.464	−0.060	0.034	0.013
3	Motor Planning	0.028	0.019	.075	−0.034	0.026	0.164
4	Extrastriate Visual	−0.016	0.023	.296	−0.028	0.032	0.241
5	Left Executive Function	0.021	0.018	.183	−0.052	0.025	0.033
6	Auditory and Speech	0.000	0.017	.996	−0.008	0.023	0.728
7	Memory Consolidation	0.015	0.017	.331	−0.034	0.023	0.157
8	Primary Visual	−0.008	0.035	.614	−0.033	0.049	0.171
9	Central Executive Function	−0.012	0.021	.456	−0.066	0.030	0.006
10	Affect Processing	−0.018	0.022	.252	−0.036	0.030	0.134
11	Motor Execution	−0.007	0.016	.668	−0.054	0.022	0.023
12	Sensorimotor	−0.021	0.017	.180	−0.054	0.024	0.026
13	Right Executive Function	0.010	0.014	.517	−0.029	0.019	0.235
14	Fronto-Cingular	0.002	0.011	.880	−0.043	0.016	0.072
15	Cerebellum	−0.011	0.011	.485	−0.042	0.016	0.079
16	Frontopolar	−0.014	0.016	.341	−0.024	0.022	0.309
17	Auditory/Language	**0.031**	**0.018**	**.045**	**−0.064**	**0.026**	**0.007**
18	Cortico-Striatal	−0.019	0.010	.196	−0.063	0.015	0.009
19	Primary Visual	−0.015	0.028	.356	−0.023	0.039	0.124
20	Posterior Default Mode	−0.010	0.016	.540	−0.039	0.022	0.109
21	Prefrontal + "What" Pathway	0.003	0.014	.858	−0.043	0.020	0.072

See Supplementary Table 1 for descriptions of all 21 independent neural networks. . Estimates that survive correction are indicated by bold text. Model I: '650 G Carrier Status + Age + Sex + Education + Social Class + Family History AD + *APOE* ε4 status. Model II: '650 G Carrier Status + Sex + '650 G Carrier Status*Sex + Age Group + Education + Social Class + Family History AD + *APOE* ε4 status. No age interactions were observed in a separate model.

Table 4.

Age, Sex, and TOMM40 ‘650 interactions among participants with APOE ε4

		Women		Men	
IC	**Neural Network**	**‘650 non-G carrier**	**‘650 G carrier**	**‘650 non-G carrier**	**‘650 G carrier**
1	Default Mode	**−0.018 ± 0.004**	**−0.013 ± 0.002**	−0.010 ± 0.006	**−0.023 ± 0.003**
2	“Where and “What” Pathways	**−0.024 ± 0.006**	**−0.012 ± 0.003**	−0.006 ± 0.006	**−0.013 ± 0.003**
4	Extrastriate Visual	**−0.031 ± 0.006**	**−0.022 ± 0.003**	−0.005 ± 0.005	**−0.022 ± 0.003**
8	Primary Visual	**−0.042 ± 0.008**	**−0.029 ± 0.004**	−0.007 ± 0.009	**−0.028 ± 0.004**
9	Central Executive Function	**−0.025 ± 0.005**	**−0.015 ± 0.003**	−0.004 ± 0.006	**−0.012 ± 0.003**
10	Affect Processing	**−0.026 ± 0.005**	**−0.013 ± 0.002**	−0.009 ± 0.006	**−0.013 ± 0.003**
11	Motor Execution	**−0.014 ± 0.003**	**−0.008 ± 0.002**	−0.007 ± 0.004	**−0.013 ± 0.002**
12	Sensorimotor	**−0.025 ± 0.004**	**−0.014 ± 0.002**	−0.009 ± 0.005	**−0.015 ± 0.002**
13	Right Executive Function	**−0.013 ± 0.003**	**−0.007 ± 0.002**	−0.005 ± 0.004	**−0.009 ± 0.002**
14	Fronto-Cingular	**−0.015 ± 0.003**	**−0.010 ± 0.001**	−0.005 ± 0.003	**−0.012 ± 0.001**
15	Cerebellum	**−0.017 ± 0.002**	**−0.007 ± 0.001**	−0.005 ± 0.003	**−0.010 ± 0.001**
16	Frontopolar	**−0.022 ± 0.003**	**−0.017 ± 0.002**	**−0.011 ± 0.005**	**−0.021 ± 0.002**
17	Auditory/Language	**−0.029 ± 0.004**	**−0.017 ± 0.002**	−0.010 ± 0.005	**−0.015 ± 0.002**
18	Cortico-Striatal	**−0.020 ± 0.002**	**−0.011 ± 0.001**	−0.007 ± 0.002	**−0.013 ± 0.011**
19	Primary Visual	**−0.021 ± 0.006**	**−0.015 ± 0.003**	−0.004 ± 0.007	**−0.021 ± 0.003**
20	Posterior Default Mode	**−0.022 ± 0.004**	**−0.015 ± 0.002**	−0.006 ± 0.004	**−0.015 ± 0.002**

Bolded text denotes p<.001 for fit lines of sub-groups. Beta values are mean ±standard deviation. Only neural networks with significant TOMM40 ‘650 x age x sex interactions (p<.001) are reported.