Characterizing the structural covariance network in AD-susceptible single nucleotide polymorphisms and the correlations with cognitive outcomes

Hsin-I Chang

Chang Gung Memorial Hospital Kaohsiung Branch

Yu-Tzu Chang

National Cheng Kung University Medical Center: National Cheng Kung University Hospital

Chi-Wei Huang

Chang Gung Memorial Hospital Kaohsiung Branch

Kuo-Lun Huang

Chang Gung Memorial Hospital Linkou Main Branch: Chang Gung Memorial Hospital

Jung-Lung Hsu

Chang Gung Memorial Hospital Linkou Main Branch: Chang Gung Memorial Hospital

Shih-Wei Hsu

Chang Gung Memorial Hospital Kaohsiung Branch

Shih-Jen Tsai

National Yang Ming University Hospital

Wen-Neng Chang

Chang Gung Memorial Hospital Kaohsiung Branch

Chen-Chang Lee

Chang Gung Memorial Hospital Kaohsiung Branch

Shu-Hua Huang

Chang Gung Memorial Hospital Kaohsiung Branch

Chiung-Chih Chang (✉ neur099@adm.cgmh.org.tw)

Chang Gung Memorial Hospital Kaohsiung Branch <https://orcid.org/0000-0002-6721-2556>

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Abstract

Background

The clinical manifestations of Alzheimer disease (AD) are related to brain network degeneration, while genetic differences may mediate network change patterns. A number of AD-susceptible loci have been reported using genome-wide association studies, however, how they modulate intracerebral volume and relationships to cognitive outcomes remains to be established. We hypothesized that different genotype groups may modulate large-scale brain networks independently or interact with apolipoprotein E4 (*ApoE4*) status to determine neurobehavior test scores.

Methods

Gray matter structural covariance networks were constructed in 324 patients with AD using T1 magnetic resonance imaging with independent component analysis (ICA). We assessed 15 genetic loci (rs9349407, rs3865444, rs670139, rs744373, rs3851179, rs11136000, rs3764650, rs610932, rs6887649, rs7849530, rs4866650, rs3765728, rs34011, rs6656401, rs597668) using the additive, recessive and dominant model on clinical outcomes. Statistical analysis was performed to explore the independent role of each locus, interactions with *ApoE4* status, and relationships to brain ICA network integrity score. We used Cognitive Abilities Screening Instrument (CASI) total score or short-term memory (STM) subscore as the major outcome factors, adjusted for covariates of education, disease duration and age.

Results

Clinically, the *CD2AP* G allele showed a protective role in CASI-total and CASI-STM scores independently or via interactions with non-*ApoE4* status, while the *CR1* A genotype group was associated with lower STM independently of *ApoE4* status. Three loci showed synergic interactions with *ApoE4*: *BIN1* T allele and *MS4A6A* G allele with non-*ApoE4* status, and *FTMT* G allele with *ApoE4* status. The network integrity scores revealed 9 significant ICA networks (anterior and posterior hippocampus, right temporal, right or left thalamus, inferior cerebellum, medial cerebellum, default mode network, frontal attention network) that correlated with cognitive scores, in which only the *ApoE4* and *MS4A6A* genotype group was independently related to the hippocampus network. Genetic loci of *MS4A6A*, *BIN1*, *CD2AP*, *CD33*, *CLU*, *BIN1*, *P73*, *EXOC3L2*, *CR1* and *MS4AE4* exerted network influence independently or via interactions with *ApoE4* status.

Conclusions

This study suggests that AD-susceptible loci may exert clinical significance independently, through interactions with *ApoE4* status or by modulating ICA networks to determine cognitive outcomes.

Background

Alzheimer disease (AD) is a complex disease. For late-onset AD, the apo-lipoprotein E (ApoE) gene represents the most significant example of a single nucleotide polymorphism (SNP) that modifies AD susceptibility (Singh, Singh et al. 2006). The clinical significance of SNPs on brain integrity has been shown in studies exploring the effect of *ApoE4* allele in people with AD (Martins, Oulhaj et al. 2005), those with mild cognitive impairment (Risacher, Kim et al. 2013), and non-demented elderly (Bretsky, Guralnik et al. 2003, Wisdom, Callahan et al. 2011). The presence of the *ApoE4* allele (Corder, Saunders et al. 1993) remains the greatest risk factor for AD (Farrer, Cupples et al. 1997), responsible for a 3- to 15-fold increase in risk. The synergic effect of the *ApoE4* allele with other genetic loci has been reported in previous studies (Mahley 1988), which showed that overall pathological cascades may influence the neuropsychiatric outcomes (Hall, Wiechmann et al. 2014). Although genetic effects have been extensively studied, only a few have shown reproducible results.

Recent large-scale genome-wide association studies (GWASs) have revealed a number of SNPs other than *ApoE4* that are also associated with AD susceptibility. A total of 19 GWAS loci have been identified using a discovery sample of 17,008 AD patients and 37,154 controls, followed by replication with 8,572 AD patients and 11,312 controls (Lambert, Ibrahim-Verbaas et al. 2013). In 2019, a GWAS meta-analysis reported an additional 29 risk loci (Jansen, Savage et al. 2019). Collectively termed as AD susceptible genes, they can only explain a small proportion of the heritability and influence of SNPs for risk prediction, and the results have been inconsistent among different ethnicities. For example, the rs111360000 polymorphism in the clusterin (*CLU*) gene has been found to be significantly associated with AD (Zhu, Liu et al. 2018) in Caucasian and Asian populations, but not people of African or Hispanic descent (Du, Tan et al. 2016). The genetic-intracerebral interactions may be different among different ethnicities, and so the genetic effect on cognitive outcomes may also be different. For AD, structural imaging is considered to be the most robust tool to reveal correlations with cognitive measures, while links between reported genotype groups and neuroimaging biomarkers may help to understand the intracerebral modulations of these SNPs. The clinical significance of these risk loci and their interactions with brain networks may also help to understand the neurobiology of AD.

Recent research suggests that highly related regions show covariance in morphometric characteristics, so-called structural covariance. Structural covariance networks (SCNs) have been associated with structural and functional connectivity, while genetic variations, developmental, degenerative and disease staging have been shown to be important covariates of interest (Alexander-Bloch, Giedd et al. 2013). The SCN is considered to be a reproducible and heritable model that may represent disease-related or genetic-associated changes in topology (Huang, Hsu et al. 2017, Chang, Chang et al. 2018, Chang, Tsai et al. 2018, Chang, Chang et al. 2019). In theory, AD susceptible genes may have greater covariance in gray matter (GM). Using spatial independent component analysis (ICA), the structural covariance between topographically distant regions can be modeled without *a priori* knowledge (Biswal, Yetkin et al. 1995, Biswal, Mennes et al. 2010). In addition to fully automated spatial component maps of maximal statistical independence maps, a network integrity score can be calculated for each ICA map. The network integrity score describes the strength of the individual expression in each network, and a higher network integrity score indicates stronger individual expression of the identified network (Beckmann and Smith 2004, Segall, Allen et al. 2012). Once an SCN pattern has been identified to distinguish one group from another, its expression can be prospectively quantified on an individual basis and correlated with the clinical or physiological

measures of interest. The SNP-brain relationships modelled by ICA can be used to test the co-variation of GM between genotype groups, while the network integrity score can be used as a dependent variable to test the genetic interactions.

In this study, we tested whether SCNs constructed using ICA could serve as an endophenotype for cognitive test outcomes in AD patients. Based on GWAS results, we assessed 15 AD-associated SNPs belonging to the following genetic loci: *CD2AP* (rs9349407), *CD33* (rs3865444), *MS4AE4* (rs670139), *BIN1* (rs744373), *PICALM* (rs3851179), *CLU* (rs11136000), *ABCA7* (rs3764650), *MS4A6A* (rs610932), *FTMT* (rs6887649), *SPTLC1* (rs7849530), *Intergenic SNP* (rs4866650), *p73* (rs3765728), *FGF1* (rs34011), *CR1* (rs6656401) and *EXOC3L2* (rs597668). We tested the independent effect of each SNP on cognitive outcomes and evaluated whether the associations were related to interactions with the *ApoE4* genotype. The clinical significance of individual SNPs or interactions between the SNP and *ApoE4* on SCN was calculated and validated by correlating the network integrity score and cognitive scores.

Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The study participants were treated at the Cognition and Aging Center, Department of General Neurology, Kaohsiung Chang Gung Memorial Hospital. The multi-disciplinary team was composed of behavior neurologists, psychiatrists, neuropsychologists, neuroradiologists and experts in nuclear medicine. We enrolled patients with AD who were diagnosed according to the International Working Group-2 criteria (Dubois, Feldman et al. 2014), and further confirmed by amyloid imaging (TW-ADNI: <http://tadni.cgmh-mi.com/home>) if the consensus panel did not agree on the diagnosis. All of the patients were in a stable condition under acetylcholine esterase inhibitor treatment from the time of diagnosis. The exclusion criteria were a past history of clinical stroke, a negative amyloid scan, a modified Hachinski ischemic score >4 and depression. After checking the inclusion and exclusion criteria, a total of 324 subjects (152 males, 172 females) were included and underwent imaging and genetic tests.

Clinical and Neurobehavioral Assessments

After enrolment, the demographic data of each patient were recorded. We also recorded the time of the first symptom. A trained neuropsychologist administered the neurobehavioral tests using Cognitive Abilities Screening Instrument (CASI) total scores as a global assessment of cognitive function. The CASI contains nine subdomains. We used attention, verbal fluency, abstract thinking, and mental manipulation subdomain scores to assess executive function (Huang, Chang et al. 2013), and orientation, short- and long-term memory, language ability, and drawing as non-executive domains. As the salient feature of AD is short-term memory (STM) impairment, we used the CASI-STM subscore as the major outcome for genetic correlations.

Genotyping

SNP genotyping was performed using MassARRAY technology with iPLEX Gold chemistry (Agena Bioscience, San Diego, CA, USA). The PCR primers and single-base-extension primers were designed using Assay Design Suite v2.0 software. The genotyping analysis was performed using an iPLEX Gold Reagent Kit according to the manufacturer's instructions. Briefly, 1 µl of DNA sample (10 ng/µl) was subjected to 5 µl of PCR reaction containing 0.2 units of Taq polymerase, 2.5 pmol each of the PCR primers and 25 mM each of the dNTPs. Thermocycling was started at 94°C for 2 min followed by 45 cycles of 94°C for 30 s, 56°C for 30 s and 72°C for 1 min, and a final extension was done at 72°C for 1 min. Unincorporated dNTPs were dephosphorylated by 0.3 U of shrimp alkaline phosphatase. Purified amplicons were then subjected to primer extension using an iPLEX Gold Reagent Kit. Primer extension was performed with a cycling program of 94°C for 30 s, followed by 40 cycles of 94°C for 5 s, and 5 cycles of 52°C for 5 s and 80°C for 5 s within 40 cycles, followed by a final extension at 72°C for 3 min. The extended reaction products were purified by cation exchange resins and then spotted onto a 384-format SpectroCHIP II array using a MassArray Nanodispenser RS1000. Mass determination was done on a MassARRAY Compact Analyzer. The resulting spectra were processed and alleles called with MassARRAY Typer 4.0 with model-based cluster analysis to analyze the genotypes of the SNPs. We tested 15 SNPs (rs9349407, rs3865444, rs670139, rs744373, rs3851179, rs11136000, rs3764650, rs610932, rs6887649, rs7849530, rs4866650, rs3765728, rs34011, rs6656401, rs597668). The risk alleles and minor allele frequencies (MAFs) are listed in Supplementary Table 1. The *ApoE* genotype was determined using rs7412 and rs429358. *ApoE4* carriers were defined as those with one or two E4 alleles.

Image Acquisition

Magnetic resonance images were acquired using a 3.0T magnetic resonance imaging (MRI) scanner (Excite, GE Medical Systems, Milwaukee, WI, USA). All MRI images were performed within 3 months of cognitive test scores. High-resolution structural images were acquired for spatial normalization using the following protocols: a T1-weighted, inversion-recovery-prepared, three-dimensional, gradient-recalled acquisition in a steady-state sequence with a repetition time/echo time/inversion time of 8,600 ms/minimal/450 ms, a 256 × 256 mm field of view, and a 1-mm slice sagittal thickness with a resolution of 0.5 × 0.5 × 1 mm³.

Data Analysis for Neuroimaging Biomarkers

Image preprocessing and statistical analysis were performed using SPM12 (Wellcome Trust Centre of Cognitive Neurology, University College London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>). The T1 images were reoriented, realigned, and normalized using the standard Montreal Neurological Institute space. The images were then segmented into GM and white matter. Related tissue segments were used to create a custom template using the diffeomorphic anatomical registration using exponentiated lie algebra approach, which is one of the highest ranking registration methods in patients with AD (Cuingnet, Gerardin et al. 2011). The modulated and warped images were then smoothed using a Gaussian kernel of 8 mm full width at half maximum.

The preprocessed spatial normalized modified T1 images from the patients were concatenated to form a subject series and entered into the ICA process. Spatial ICA was carried out using Multivariate Exploratory Linear Optimized Decomposition into Independent Components software package version 3.15 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC>). The resulting independent components were z-transformed and visualized using a threshold of $z > 1.96$ ($p <$

0.05). Differences in ICA intensities between groups in each SNP were calculated. In addition, interactions between individual SNPs and *ApoE4* status were also modelled using a general linear model, corrected for age, educational level, gender and disease duration (years). To understand the clinical significance of the identified SCN in the patients, we also calculated partial correlations between the extracted SCN intensity and the clinical scores by setting the significance value at $p < 0.05$ using Bonferroni correction for multiple comparisons and covariates of age, educational level and disease duration (years).

Statistical Analysis

Clinical and laboratory data were expressed as mean $\pm$ standard deviation. The Student's t test was used to compare continuous variables, and the chi-square test was used for categorical variables. Linear regression models of associations between the cognitive scores and 15 selected AD-related SNPs were analyzed, adjusting for education, age and duration of disease. All statistical analyses were conducted using SPSS software (SPSS version 22 for Windows®, SPSS Inc., Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

Demographic Data of the AD Patients

The demographic data and cognitive test scores are shown in Table 1. The mean duration of disease was 0.9 ± 1.12 years, and 114 cases were E4 carriers (E4 homozygote $n = 14$). The risk alleles of *CD2AP*, *ABCA7*, *FTMT*, *SPTLC1*, *FGF1*, *CR1* and *EXOC3L2* were found on the minor alleles (Supplementary Table 1). Of note, the MAFs of *FTMT* and *CR1* were extremely low.

Table 1 Demographic data of the 324 patients with Alzheimer disease	
	Case numbers or scores
Male/Female	152 / 172
Education (year)	7.8 $\pm$ 5.09
Duration of disease (year)	0.9 $\pm$ 1.12
ApoE4 carriers (%)	114 (35.19%)
Age (years)	71.6 $\pm$ 8.82
Cognition Ability Screening Instrument	
Total score (100)	68.6 $\pm$ 24.68
Executive function test (40)	25.5 $\pm$ 9.62
Attention (8)	6.3 $\pm$ 1.63
Verbal fluency (10)	5.4 $\pm$ 3.08
Abstract thinking (12)	8.1 $\pm$ 3.12
Mental manipulation (10)	5.7 $\pm$ 3.50
Non-executive domains (60)	43.2 $\pm$ 15.83
Orientation (18)	13.0 $\pm$ 5.71
Short- term memory (12)	6.1 $\pm$ 4.11
Long-term memory (10)	8.3 $\pm$ 2.42
Language ability (10)	8.1 $\pm$ 2.42
Drawing (10)	7.7 $\pm$ 2.99
Data presented as mean $\pm$ standard deviation. Numbers in parentheses indicate maximal score.	

Effect Of Independent Genotype Groups On Cognitive Outcomes

Two SNPs showed independent or synergic effects on cognitive measures. The *CD2AP* G allele was associated with CASI-total scores (Table 2) on the additive or dominant model, and the G allele was associated with higher scores. The *CD2AP* G allele (on the additive or dominant model) was also associated with a higher STM score (Table 3). The association between the *CD2AP* G allele and cognitive scores showed interactions with the non-*ApoE4* genotype in CASI-total score (Table 2) and STM score (Table 3). In the recessive model, the *CR1* A allele was associated with a lower STM score (Table 3), while the risk of a detrimental effect was independent of *ApoE4* status. Of note, the MAF of the A allele in *CR1* was 0.029.

Table 2
General linear model for single nucleotide polymorphisms on cognitive ability screening instrument total scores*

Gene	Additive model				Dominant model			Recessive Model			Interaction with APOE		
	Group	β	SE	p	β	SE	p	β	SE	p	Chi-square	p	effects
<i>CD2AP</i>	GG compares to CC (1/3)	44.091	14.17	0.002	43.245	14.165	0.002	-4.337	3.0951	0.161	5.989	< 0.05	Non-E4
rs9349407	CG compares to CC(2/3)	41.125	14.32	0.004									
<i>CD33</i>	CC compares to AA (1/3)	0.406	7.658	0.958	1.048	7.5987	0.890	1.746	2.9576	0.555	2.489	0.477	-
rs 3865444	CA compares to AA(2/3)	2.398	7.8728	0.761									
<i>MS4AE4</i>	GG compares to TT (1/3)	2.26	4.2595	0.596	4.152	3.8605	0.282	1.896	2.9644	0.522	6.002	0.112	-
s670139	GT compares to TT (2/3)	5.514	4.0691	0.175									
<i>BIN1</i>	AA compares to GG (1/3)	0.089	4.4880	0.984	1.080	4.1155	0.793	1.32	2.941	0.654	3.612	0.306	-
rs744373	AG compares to GG(2/3)	1.791	4.3096	0.678									
<i>PICALM</i>	CC compares to TT (1/3)	-3.254	4.1484	0.433	-2.431	3.7963	0.522	1.986	2.9024	0.494	3.117	0.374	-
rs3851179	CT compares to TT (2/3)	-1.733	4.0528	0.669									
<i>CLU</i>	CC compares to TT (1/3)	0.490	6.8294	0.943	1.801	6.7691	0.790	3.333	2.9119	0.252	2.972	0.396	-
rs11136000	TC compares to TT (2/3)	4.358	7.0434	0.536									
<i>ABCA7</i>	TT compares to GG (1/3)	0.127	4.4213	0.977	1.915	4.1498	0.644	2.657	2.8650	0.354	3.034	0.386	-
rs3764650	TG compares to GG(2/3)	3.636	4.4014	0.409									
<i>MS4A6A</i>	GG compares to TT (1/3)	-1.407	4.2567	0.741	0.329	3.8545	0.932	2.588	2.9492	0.380	4.623	0.202	-
rs10932	TG compares to TT (2/3)	1.562	4.0599	0.7									
<i>FTMT</i>	AA compares to GG (1/3)	26.705	24.7683	0.281	26.328	24.7763	0.288	2.905	3.8570	0.451	2.337	0.126	-
rs6887649	AG compares to GG(2/3)	24.296	24.9768	0.331									
<i>SPTLC1</i>	AA compares to GG (1/3)	11.770	12.4733	0.345	11.596	12.4562	0.352	1.663	3.5659	0.641	2.738	0.434	-
rs7849530	AG compares to GG(2/3)	10.829	12.8078	0.398									
<i>Intergenic SNP</i>	AA compares to CC (1/3)	-4.298	8.0343	0.593	-4.654	7.9625	0.559	-0.533	2.9044	0.854	3.990	0.263	-
rs4866650	AC compares to CC(2/3)	-5.279	8.1853	0.519									
<i>P73</i>	GG compares to AA (1/3)	-0.260	4.2196	0.951	1.091	2.9254	0.709	1.076	3.9070	0.783	3.319	0.345	-
rs3765728	GA compares to AA(2/3)	1.606	3.1456	0.610									
<i>FGF1</i>	GG compares to AA (1/3)	-6.776	4.5323	0.144	-5.592	4.4370	0.208	3.584	2.8329	0.206	5.267	0.153	-

*adjusted for education, disease duration and age

SE: standard error;

Gene	Additive model	Dominant model			Recessive Model				Interaction with APOE				
rs34011	GA compares to AA(2/3)	-4.123	4.7375	0.384									
CR1	AA compares to GG (1/3)	34.971	24.7119	0.157	34.67	24.7429	0.161	-7.488	6.1687	0.225	3.999	0.135	-
rs6656401	GA compares to GG(2/3)	-5.771	6.3347	0.362									
EXOC3L2	TT compares to CC (1/3)	-2.806	4.3082	0.515	-4.447	3.9970	0.266	-1.65	2.8892	0.568	2.783	0.426	-
rs597668	TC compares to CC(2/3)	-5.899	4.2413	0.164									
*adjusted for education, disease duration and age													
SE: standard error;													

Table 3
General linear model for single nucleotide polymorphisms on cognitive ability screening instrument short-term memory score*

Gene	Additive model				Dominant model			Recessive Model			Interaction with APOE		
	Group	β	SE	p	β	SE	p	β	SE	p	Chi-square	p	effects
<i>CD2AP</i>	GG compares to CC (1/3)	5.596	2.3663	0.018	5.418	2.3673	0.022	-0.790	0.5135	0.124	7.950	0.019	Non-E4
rs9349407	CG compares to CC(2/3)	4.971	2.3903	0.038									
<i>CD33</i>	CC compares to AA (1/3)	1.086	1.2685	0.392	1.225	1.2594	0.331	0.277	0.4910	0.573	5.597	0.133	-
rs 3865444	CA compares to AA(2/3)	1.518	1.3042	0.244									
<i>MS4AE4</i>	GG compares to TT (1/3)	0.506	0.7078	0.475	0.675	0.6407	0.292	0.095	0.4923	0.847	6.163	0.104	-
s670139	GT compares to TT (2/3)	0.797	0.6762	0.239									
<i>BIN1</i>	AA compares to GG (1/3)	0.488	0.7432	0.511	0.238	0.6819	0.727	-0.442	0.4869	0.364	7.7977	0.046	E4
rs744373	AG compares to GG(2/3)	0.059	0.7136	0.934									
<i>PICALM</i>	CC compares to TT (1/3)	0.035	0.6895	0.960	0.087	0.6308	0.890	0.061	0.4823	0.899	6.756	0.080	-
rs3851179	CT compares to TT (2/3)	0.132	0.6736	0.845									
<i>CLU</i>	CC compares to TT (1/3)	0.024	1.1313	0.983	0.268	1.1236	0.811	0.758	0.4824	0.116	6.739	0.081	-
rs11136000	TC compares to TT (2/3)	0.837	1.1667	0.473									
<i>ABCA7</i>	TT compares to GG (1/3)	1.112	0.7320	0.129	1.159	0.6856	0.091	-0.190	0.4760	0.690	6.606	0.086	-
rs3764650	TG compares to GG(2/3)	1.204	0.7287	0.098									
<i>MS4A6A</i>	GG compares to TT (1/3)	0.509	0.7056	0.470	-0.117	0.6389	0.855	0.632	0.4888	0.196	8.070	0.045	Non-E4
rs10932	TG compares to TT (2/3)	0.162	0.6730	0.809									
<i>FTMT</i>	AA compares to GG (1/3)	5.961	4.1087	0.147	-5.954	4.1075	0.147	0.161	0.6410	0.802	4.598	0.032	E4
rs6887649	AG compares to GG(2/3)	5.921	4.1433	0.153									
<i>SPTLC1</i>	AA compares to GG (1/3)	1.145	2.0743	0.581	1.198	2.0720	0.563	0.188	0.5928	0.751	6.861	0.076	-
rs7849530	AG compares to GG(2/3)	1.429	2.1299	0.502									
<i>Intergenic SNP</i>	AA compares to CC (1/3)	0.597	1.3297	0.653	-0.853	1.3220	0.519	-0.594	-0.4811	0.217	5.203	0.158	-
rs4866650	AC compares to CC(2/3)	1.302	1.3547	0.337									
<i>P73</i>	GG compares to AA (1/3)	0.545	0.7934	0.438	-0.424	0.4876	0.385	0.353	0.6516	0.588	6.753	0.080	-
rs3765728	GA compares to AA(2/3)	0.378	0.5244	0.471									
<i>FGF1</i>	GG compares to AA (1/3)	0.372	0.7702	0.629	-0.299	0.7369	0.685	0.212	0.4705	0.653	4.551	0.208	-

*adjusted for education, disease duration and age

SE: standard error;

Gene	Additive model	Dominant model			Recessive Model					Interaction with APOE			
rs34011	GA compares to AA(2/3)	0.208	0.7877	0.792									
<i>CR1</i>	AA compares to GG (1/3)	5.587	4.0857	0.171	5.483	4.1096	0.182	-2.217	1.0189	0.030	4.670	0.198	-
rs6656401	GA compares to GG(2/3)	2.006	1.0473	0.055									
<i>EXOC3L2</i>	TT compares to CC (1/3)	0.131	0.7166	0.855	-0.115	0.6647	0.862	-0.382	0.4793	0.425	7.655	0.054	-
rs597668	TC compares to CC(2/3)	0.333	0.7055	0.637									
*adjusted for education, disease duration and age													
SE: standard error;													

Effect of Interactions with the ApoE4 Gene on STM Scores

Three SNPs showed interactions with the *ApoE4* gene: *BIN1*, *MS4A6A* and *FTMT*. The risk allele of *BIN1* T allele and *FTMT* G allele showed interactions with the E4 allele, while the *MS4A6A* G allele showed a protective role via interactions with non-E4 alleles. The MAF of the G allele in *FTMT* was 0.082.

Network Topography And Clinical Significance Validation

To understand the effects of SCN and SNP genotype groups, a total of 20 ICA components were constructed. For each SNP, we compared network integrity score between SNP genotype groups (Supplementary Table 2). The stratification of each SNP genotype group was based on the number of cases and the balance of Hardy-Weinberg equilibrium. The spatial extent of 15 ICA modes showing genotypic differences is shown in Fig. 1.

Using network integrity scores, we correlated each significant ICA with cognitive tests (Table 4) to establish network significance. The CASI scores were classified as indicating general cognitive performance (CASI-total score), executive domains and non-executive domains. The anterior hippocampus, posterior hippocampus, right temporal, right thalamus, left thalamus, inferior cerebellum default mode network and frontal attention network were significantly related to CASI-total scores. For correlations with executive domains scores, the network patterns overlapped with the general performance network except for default mode network and inferior cerebellum. The topography of non-executive networks overlapped with the CASI-total score network. Meanwhile, the network integrity scores of supplementary motor area (SMA) and postcentral gyrus were inversely correlated with STM.

Table 4
Significant relationships between independent component analysis and cognitive test scores

Area		Gene and SNP	CASI	Executive Domains				Non-executive Domains		
Index On Figure 1	Network Main Structure		Total scores	Attention	Verbal fluency	Abstract thinking	Mental manipulation	Orientation	Short-term memory	Long-term memory
A	Basal Ganglia	CLU (Rs11136000) FGF1 (rs34011) APOE4 * PICALM (rs3851179)	-0.063	-0.036	-0.096	-0.094	-0.069	-0.023	-0.072	-0.035
B	Anterior Hippocampus	APOE APOE * MS4AE4 (rs670139) APOE * MS4A6A (rs610932) APOE * P73 (rs3765728) APOE * CR1 (rs6656401)	0.315(**)	0.084	0.121(*)	0.188(**)	0.222(**)	0.387(**)	0.365(**)	0.280(**)
C	Posterior Hippocampus	APOE MS4A6A (rs610932) APOE * MS4AE4 (rs670139) APOE * BIN1 (rs744373) APOE * PICALM(rs3851179) APOE * MS4A6A (rs610932) APOE * CR1 (rs6656401) APOE * EXOC3L2 (rs597668)	0.434(**)	0.217(**)	0.338(**)	0.279(**)	0.262(**)	0.460(**)	0.492(**)	0.314(**)
D	Right Temporal	MS4A6A (rs610932) APOE * FTMT (rs6887649)	0.351(**)	0.177(**)	0.233(**)	0.237(**)	0.275(**)	0.337(**)	0.357(**)	0.300(**)
E	Right Thalamus	MS4A6A (rs610932)	0.167(**)	0.128(*)	0.138(*)	0.192(**)	0.075	0.129	0.123(*)	0.113(*)
F	Left Thalamus	BIN1 (rs744373)	0.128(*)	0.116(*)	0.115(*)	0.157(**)	0.058	0.105	0.126 (*)	0.051

Numbers under the cognitive test name represent partial correlation coefficient, adjusted for age, disease duration and education.

Area		Gene and SNP	CASI	Executive Domains				Non-executive Domains		
G	Postcentral Gyrus	APOE	-0.082	-0.005	-0.106	-0.020	-0.028	-0.109	-0.121(*)	-0.033
		CD2AP (rs9349407)								
		APOE * CD2AP (rs9349407)								
		APOE * CD33 (rs3865444)								
		APOE * MS4AE4 (rs670139)								
		APOE * PICALM(rs3851179)								
		APOE * ABCA7 (rs3764650)								
		APOE * MS4A6A (rs610932)								
		APOE * SPTLC1 (rs7849530)								
		APOE * P73 (rs3765728)								
		APOE * CR1 (rs6656401)								
		APOE * EXOC3L2 (rs597668)								
H	Supplementary Motor Cortex	APOE	-0.072	-0.016	-0.074	-0.071	-0.074	-0.085	-0.114(*)	-0.029
		CD33 (rs3865444)								
		CLU (rs11136000)								
		P73 (rs3765728)								
		APOE * CD33 (rs3865444)								
		APOE * CLU (rs11136000)								
		APOE * MS4AE4 (rs670139)								
		APOE * MS4A6A (rs610932)								
		APOE * P73 (rs3765728)								
		APOE * FGF1 (rs34011)								
		APOE * EXOC3L2 (rs597668)								
I	Inferior Cerebellum	BIN1 (rs744373)	0.126(*)	-0.084	-0.093	-0.069	-0.051	-0.136(*)	-0.136(*)	-0.163(**)
J	Lateral Cerebellum	SPTLC1 (rs7849530, rs4866650)	-0.015	0.029	0.022	0.043	-0.035	-0.043	-0.030	-0.018
K	Medial Cerebellum	EXOC3L2 (rs597668)	0.151(**)	-0.080	-0.131(*)	-0.110	-0.079	-0.150(**)	-0.096	-0.178(**)
L	Default Mode Network	CLU (rs11136000)	-0.117(*)	0.096	0.088	0.072	0.086	0.150(**)	0.143(*)	0.051
		BIN1 (rs744373)								
M	Frontal Attention Network	CR1 (rs6656401)	0.211(**)	0.164(**)	0.198(**)	0.186(**)	0.142(*)	0.191(**)	0.176(**)	0.115(*)
		APOE * EXOC3L2 (rs597668)								

Numbers under the cognitive test name represent partial correlation coefficient, adjusted for age, disease duration and education.

Area		Gene and SNP	CASI	Executive Domains				Non-executive Domains		
N	Cerebellum	MS4AE4 (rs670139)	-0.063	-0.040	-0.145(*)	-0.032	-0.040	-0.059	-0.030	-0.029
O	Cingulate Network	ABCA7 (rs3764650)	-0.041	0.060	0.067	0.006	0.011	0.041	0.030	0.049

Numbers under the cognitive test name represent partial correlation coefficient, adjusted for age, disease duration and education.

Network Effect for ApoE4, Preselected SNP and Genetic-ApoE4 Interactions

Significant differences between *ApoE4* and non-E4 carriers in network intensity scores were identified in anterior and posterior hippocampus (Fig. 1B, 1C), postcentral gyrus (Fig. 1G) and SMA (Fig. 1H).

A number of networks showed SNP-*ApoE4* interactions (Table 4, Fig. 1A-D, G, H, M). These networks included cardinal networks of AD, including anterior and posterior hippocampus, right temporal, postcentral gyrus, frontal executive network and supplementary motor cortex. All preselected SNPs interacted with *ApoE4* status in the abovementioned networks except *CLU*. Among the 15 networks, only basal ganglia (Fig. 1A), lateral cerebellum (Fig. 1J) and cingulate network (Fig. 1O) showed no correlations with clinical scores.

A number of SNPs exerted a network influence independently from *ApoE4*, including *MS4A6A*, *BIN1*, *CD2AP*, *CD33*, *CLU*, *BIN1*, *P73*, *EXOC3L2*, *CR1* and *MS4AE4*. Independent roles were observed for *CLU* on basal ganglia, SMA and default mode network (Fig. 1A, 1H, 1L), *FGF1* on basal ganglia (Fig. 5A), *MS4A6A* on hippocampus and temporal, thalamus (Fig. 5C-E), *BIN1* on left thalamus, cerebellum, default mode network (Fig. 1F, 1I, 1L), *CD2AP* on post-central gyrus (Fig. 1G), *CD33* and *p73* on SMA (Fig. 1H), *CR1* on frontal attention network (Fig. 1M), and *ABCA7* on cingulate network (Fig. 1O).

Discussion

Major Findings

In this study, we explored the clinical significance of 15 AD-susceptible loci by constructing SCNs using an ICA approach in patients with AD. Our results reflected complex interactions among preselected SNPs, brain network integrity and cognitive outcomes in which the mechanisms were via different pathways. First, the SCN served as the endophenotype in predicting individual genotype groups in cognitive outcomes. For SCN as the endophenotype, the genotype group either exerted an independent role or synergistic interactions with *ApoE4* status on cognitive measures. The SCNs showing clinical significance included the hippocampal axis, temporal, thalamus, default mode network and frontal attention network. As the SCNs were each associated with different cognitive domains, the identification of genotype-SCN relationships may help to understand the neurobiology in AD. Second, for genetic-clinical relationships, our results suggested that the main genotype effect on cognitive measures was via interactions with *ApoE4* status. This included protective *CD2AP* G allele and *MS4A6A* G allele with non-*ApoE4* interactions, and risk allele of *BIN1* T allele and *FTMT* G allele with *ApoE4* status. Of note, independent roles of genotype groups (*CD2AP* and *CR1*) on cognitive outcomes were also found. However, as *CR1* risk allele A was a minor allele with a low MAF, the *CR1* finding here should be interpreted with caution.

ApoE4 Modulated Hippocampal SCN and Determined the Salient Feature of AD

By definition, the SCN is based on the similarity of the same microstructural variations and thus may be influenced by factors influencing underlying structures such as the expression of common genetic traits during development. The independent role of *ApoE4* on the hippocampal and SMA SCN was established in this study. As the hippocampal SCN intensity score was also correlated with STM score in our AD patients, this finding supports the role of *ApoE4* in linking salient cognitive and biosignature features in AD.

Traditional cytoarchitectonic distribution of the hippocampus (Frederickson, Klitenick et al. 1983) is a convoluted GM structure encompassing three architectonically distinct regions: the fascia dentata, the CA region (which can be subdivided into CA1–CA4 fields), and the subicular complex. In this study, two hippocampus SCNs in ICA (anterior versus posterior hippocampus) showed *ApoE4* genotype group differences. The SCN of the hippocampus axis associated with *ApoE4* showing the anterior-posterior axis is consistent with task-related activities or connectivity patterns (Colombo, Fernandez et al. 1998, Przewdzik, Faber et al. 2019). A similar anterior-posterior organization has recently been reported, suggesting that the gene expression is linked to the distinct molecular gradient in the hippocampus (Vogel, La Joie et al. 2020). Among the 15 preselected SNPs and *ApoE4*, only *ApoE4* showed an independent role in the entire hippocampal axis. The association with cognitive test scores in hippocampal SCN intensity scores and the interactions between hippocampus and cortical/subcortical structures demonstrate its tight integration within the large-scale degenerative system, so that hippocampus-*ApoE4* is the most important factor in predicting AD functional severity.

ApoE4 Interacted with MS4A, CR1, PICALM, p73, BIN1 and EXOC3L2 on the Hippocampal Axis

Our results showed the role of *MS4A6A* (rs610932) on posterior hippocampus axis. In addition, *MS4A4E* and *MS4A6A* also interacted with *ApoE4* in the entire hippocampal SCN, similar to that reported in a smaller AD cohort (Chang, Mori et al. 2019). A previous study reported interactions between *MS4A* and *CLU* (Lambert, Ibrahim-Verbaas et al. 2013) or *CD33* on conferring the risk of AD. Common variants of *MS4A6A* (rs610932), along with *MS4A4E* (rs670139), *CD33* (rs3865444) and *CD2AP* (rs9349407), *CLU* and *PICALM* have been associated with memory decline (Hollingworth, Harold et al. 2011, Naj, Jun et al. 2011, Karch, Jeng et al. 2012). Our results emphasize the role of the hippocampus and *MS4A* epistasis on the clinical features of AD.

The SNPs that interacted with the *ApoE4* allele on the hippocampal axis in this study may explain the mechanisms of AD susceptibility. *CR1* on chromosome 1 (rs6656401, odds ratio [OR] = 1.21, 95% confidence interval [CI] 1.14–1.29, $p = 3.7 \times 10^{-9}$) has been shown to encode complement component (3b/4b) receptor 1 (Lambert, Heath et al. 2009) which is known to participate in the clearance of β amyloid peptides in AD pathology. By facilitating the clearance of A β peptides through enhanced translocation, increased micro-vessel *PICALM* (phosphatidylinositol binding clathrin assembly protein) (rs3851179, OR = 0.86, $p = 1.3 \times 10^{-9}$) has been shown to reduce the development of AD (Harold, Abraham et al. 2009). The SNP rs3765728 within tumor protein p73 (Tao, Sun et al. 2014) has been associated with neuron survival, and has been found to have a synergetic effect with *APOE* on the risk of AD. In addition, rs744373 near *BIN1* (OR = 1.13; 95% CI, 1.06–1.21 per copy of the minor allele; $p = 1.59 \times 10^{-11}$) has been related to AD with possible mechanisms involving tau-related cascade (Franzmeier, Rubinski et al. 2019). Moreover, rs597668 is near *EXOC3L2* (OR, 1.18; 95% CI, 1.07–1.29; $p = 6.45 \times 10^{-9}$), and mutations of this gene may be associated with AD.

Dominant Model Suggested Protection of the CD2AP rs9349407 G Allele in Non-E4 Carriers

The role of rs9349407 as a risk SNP in Han Chinese people has been reported (Xiao, Liu et al. 2015), but the findings have been inconsistent (Jiao, Liu et al. 2015). One meta-analysis suggested that rs9349407 C is a risk allele for AD susceptibility in East Asian, American, Canadian, and European populations (Chen, Wu et al. 2015). In our additive or dominant model, AD patients with the rs9349407 G allele had higher CASI total and STM scores, especially the non-E4 carriers. The minor allele C of rs9349407 has been associated with neuritic plaque burden in pathology, which may explain why non-E4 carriers with the G allele may have higher cognitive test scores (Shulman, Chen et al. 2013).

In the current study, we only enrolled patients with clinical AD, and we tested whether risk or protective SNP alleles have an effect on cognitive test scores or SCNs. Although not all of our patients with AD received amyloid scans, our exclusion criteria reduced the possibility of non-AD pathologies. rs9349407 is a polymorphism in the *CD2AP* gene which translates the scaffolding molecule for signal transduction. Loss of function of *CD2AP* has been linked to enhanced A β production, tau-induced neurotoxicity, abnormal neurite structure modulation and reduced blood-brain barrier integrity, which has been implicated in AD pathogenesis (Dubey, Gulati et al. 2018, Ramos de Matos, Ferreira et al. 2018).

Modulation of Frontal Attention Network by the CR1 rs6656401 A Allele on Cognitive Outcomes

As STM is the salient feature in AD, it was used as a dependent variable in SNP genetic model analysis. In addition to rs9349407, we also identified the independent role of rs6656401 A allele on lower STM scores, consistent with a previous meta-analysis of a greater risk on the minor allele A in AD (Shen, Chen et al. 2015). *CR1* is an AD susceptibility locus that also influences AD-related traits on neuritic plaque deposition and in episodic memory decline. The coding variant in the long homologous repeat D region of the *CR1* gene, rs4844609 (Ser1610Thr) has been associated with episodic memory decline and accounts for the known effect of SNP rs6656401 (Keenan, Shulman et al. 2012). In SCN analysis in this study, the effect may have been partially modulated by interactions with *ApoE4* on the hippocampal axis.

Three studies have confirmed the association between AD susceptibility and the rs6656401 A allele in Chinese patients (Zhang, Yu et al. 2010, Chen, Kao et al. 2012, Jin, Li et al. 2012), although another study showed no association (Li, Shi et al. 2011). rs6656401 is in the *CR1* gene, and complement system activation in the clearance of amyloid has been proposed to be a possible mechanism of the risk associated with rs6656401 (Zhang, Yu et al. 2010). Although the independent role of rs6656401 minor allele on lower STM was confirmed in this study, it is worth noting that the A allele was a minor allele and the MAF was only 0.029. Therefore, the relationship with lower STM may be due to the small sample size of the A allele. To understand the effect, we also checked SCN intensity and explored whether the relationships between the rs6656401 A allele and cognitive test results were modulated by SCN. As shown in our correlation analysis, the frontal attention SCN intensity was significantly different between A carriers and G allele, and the intensity was also related to the executive and non-executive domains. Therefore, we suggest that the frontal attention network is the endophenotype of the link between rs6656401 and cognitive outcomes.

Effect of FTMT on STM in AD via ApoE4 and Default Mode Network

The intergenic SNP (rs6887649) is 10 KB upstream of ferritin mitochondrial gene (*FTMT*), which has been shown to modify the association between amyloid positivity and baseline ventricular volume (Hohman, Koran et al. 2014). From our study, the effect of FTMT on STM is via interaction with *ApoE4*, while it also modulates the default mode network. The default mode network is regarded to be an early neuroimaging bio-signature (Chang, Huang et al. 2015), and a recent report suggested that the default mode network may be comprised of multiple, spatially dissociated but interactive components (Andrews-Hanna, Reidler et al. 2010), of which two subsystems are of particular interest. Our SCN result of an association with FTMT was consistent with cores in the posterior cingulate cortex and anterior medial prefrontal cortex that is known as the “dorsal medial prefrontal cortex subsystem” (or midline core subsystem).

Limitations And Methodological Considerations

This study has several limitations. First, we enrolled subjects with early stage AD, and we did not include a control group. As the SNPs were preselected from GWAS results showing significance in AD susceptibility, the inclusion of a control group may have helped to elucidate whether these SNPs exerted similar GM modulation patterns in healthy elderly subjects as in those with AD. However, as these SNPs each exert different functional activities on the pathogenetic mechanisms in AD, the use of a pure AD population may help to maximize the effect of each SNP on regional GM networks. As a structural covariance matrix is defined by estimating the inter-regional correlations of cortical volumes between all possible pairs of regions defined by anatomy, SCN construction relies on both the spatial patterns of morphometric and signal similarities. Given the differences in brain morphometry in controls, it would be difficult to match all influential factors. Therefore, we focused on the initial hypothesis testing the endophenotypic role of SCN in cognitive outcomes. Another limitation is the estimation of the number of components for ICA analysis. Most studies have used 12 to 30 components in structural networks or resting state networks. In this study, we constructed 20 networks and filtered the clinical significance of a network using correlation analysis with cognitive measures and by matching with the ICA template (<https://brainmap.org/icsn/>). From a methodological aspect, the group-wise structural covariance analysis relied on the morphological

properties of each voxel with the rest of the brain across a group of participants. The registration of a single participant's structural data to the template involves linear and non-linear deformation that can result in inaccuracies in subregions. In this report, we emphasized the well-characterized network to explain the SNP effect where the network significance was established by correlations with cognitive measures. Finally, the use of 15 AD-susceptible SNPs to validate the underlying pathological mechanisms may have oversimplified the genetic interactions. We only tested interactions between each SNP and *ApoE4* status as *ApoE4* remains the strongest predictor. The interpretations of interactions between SNPs and SCN were based on a literature review of possible alterations in functional pathways and may not fully explain the in vivo situation. Therefore, the findings should be interpreted with caution.

Conclusion And Future Perspectives

In this study, we aimed to elucidate the major modes of structure variation in AD-susceptible SNPs and assess the SNP co-plastic properties. Our findings demonstrated AD-related SNP effects that may influence the SCN independently or synergistically with *ApoE4*. The use of SCN as an endophenotype allowed us to assume the independent and synergistic role of putative SNPs to predict cognitive measures. The complex interplay among these SNPs in our study suggests that a hierarchical order of SNPs modulate brain networks.

Abbreviations

AD Alzheimer disease

ApoE apolipoprotein E

CASI Cognitive Abilities Screening Instrument

GM gray matter

GWAS genome-wide association study

ICA independent component analysis

MAF minor allele frequency

MRI magnetic resonance imaging

SCN structural covariance network

SMA supplementary motor area

SNP single nucleotide polymorphism

STM short-term memory

Declarations

The authors have nothing to declare.

Ethics approval and consent to participate

This study was approved by the Chang Gung Memorial Hospital Ethics Committee following the standards for medical research in humans recommended by the Declaration of Helsinki. All participants gave signed, informed consent for the cognitive tests described, inclusion of samples, neuroimaging and demographic data.

Consent for publication

Not applicable

Availability of data and materials

The data analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CWH, KLH, JLH, SWH, WNC, CCL, SHH and CCC contributed to the acquisition and analysis of data. HIC, YTC and CCC drafted a significant portion of the manuscript and figures. All authors read and approved the final manuscript.

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Figures

Figure 1

Significant structural covariance network showing group differences in signal intensities using independent component analysis.

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