Molecular Neurobiology (2019) 56:4518–4529
https://doi.org/10.1007/s12035-018-1394-0

MAOA-VNTR Genotype Effects on Ventral Striatum-Hippocampus Network in Alzheimer's Disease: Analysis Using Structural Covariance Network and Correlation with Neurobehavior Performance

Hsin-I Chang[1,2] · Ya-Ting Chang[1] · Shih-Jen Tsai[3,4] · Chi-Wei Huang[1] · Shih-Wei Hsu[5] · Mu-En Liu[4] · Wen-Neng Chang[1] · Chia-Yi Lien[1] · Shu-Hua Huang[6] · Chen-Chang Lee[5] · Chiung-Chih Chang[1]

Received: 20 February 2018 / Accepted: 11 October 2018 / Published online: 18 October 2018

Abstract

Functional polymorphisms in the promoter region of the monoamine oxidase A (*MAOA*) gene are associated with brain MAOA activity and transcriptional efficiency in patients with Alzheimer's disease (AD). This study investigated structural covariance networks mediated by *MAOA*-variable number tandem repeat (*VNTR*) genotypes in patients with AD, and assessed whether this effect was associated with sex. A total of 193 patients with AD were classified into four genotype groups based on MAOA transcriptional efficiency (female low [L], low-high + high activity groups [LH + H]; male L, male H groups). Structural covariance networks were constructed focusing on triple-network and striatal networks. Covariance strength was analyzed in the four groups, and the genotype and sex main effects and their interactions were analyzed. Significant peak cluster volumes were correlated with neurobehavioral scores to establish the clinical significance. *MAOA* genotypes mediated the structural covariance strength on the dorsolateral prefrontal cortex (dLPFC)-caudate axis in both sexes, but a higher covariance strength was shown in the female L group and male H group. The independent effect of male sex was related to higher covariance strength in the frontal medial superior region in the dLPFC, dorsal caudate (DC), and ventral superior striatum (VSs) seeds. In contrast, female sex had higher covariance strength in the frontal opercular areas anchored by the dLPFC, DC, and VSs seeds. Topographies showing higher covariance strength with sex interactions were found in the male H group and female L group in the dLPFC supplementary motor axis, DC-SMA, and DC-precentral axis. In our patients with AD, *MAOA-VNTR* polymorphisms and sex had independent and interactive effects on structural covariance networks, of which the dLPFC-, VSs-, and DC-anchored networks represented major endophenotypes that determined cognitive outcomes. The sex-genotype interaction model suggested that male high activity and female low activity may modulate brain morphometric connectivity and determine cognitive scores.

Keywords Alzheimer's disease · Structural covariance · Caudate nucleus · Dorsolateral prefrontal cortex · Genetic effect · Striatal network · Monoamine oxidase A · Variable number tandem repeats

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12035-018-1394-0) contains supplementary material, which is available to authorized users.

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

[1] Department of General Neurology, Cognitive and Aging Center, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, #123, Ta-Pei Road, Niaosung, Kaohsiung County 833, Taiwan

[2] Institute of Human Resource Management, National Sun Yat-Sen University, Kaohsiung, Taiwan

[3] Psychiatric Department of Taipei Veterans General Hospital, Taipei, Taiwan

[4] Psychiatric Division, School of Medicine, National Yang-Ming University, Taipei, Taiwan

[5] Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

[6] Department of Nuclear Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

Introduction

The monoamine oxidase A (MAOA) enzyme is found solely in the neurons [1] and degrades the neurotransmitters of norepinephrine, dopamine, and serotonin. Located on the X chromosome (Xp11.23), the *MAOA* gene modulates levels of monoamine, and this has been reported to explain the sex-related interindividual vulnerability to neuropsychiatric disorders [2]. A common variable number of tandem repeat (VNTR) polymorphism in the *MAOA* promoter region has been shown to affect the transcriptional activity in vitro [3]. In a human male skin fibroblast cell line [4] and in patients with Alzheimer's disease (AD) [5], the MAOA-VNTR alleles with 3.5 and 4 repeats were found to transcribe MAOA more efficiently than those with 3 repeats. Consequently, the high activity genotype group may show higher degradation rates in monoamines and low MAOA activity.

The *MAOA-VNTR* gene is located in the sex chromosome, so the transcriptional activity of the *MAOA* gene in males and females is different. The low activity (L) group includes 2 repeats, 3 repeats, and 5 repeats in men, and 2/2, 3/3, 5/5, 2/3, 2/5, and 3/5 repeats in women. The low-high group (LH group) is only seen in women that included 2/4, 2/3.5, 3/4, 3/3.5, 5/4, 5/3.5 repeats. In the high activity group (H group), 4 repeats and 3.5 repeats have been reported in men, while 3.5/3.5, 4/4, and 4/3.5 repeats have been reported in women [6]. In group segregation, the analysis of genotype effects is designed either in one sex or by designating the female LH group into L or H groups [7]. As the expression of MAOA in heterozygous allele carriers is still unclear, some investigators have selected all-male samples and eliminated heterozygous females from their samples [8–10].

The genetic variations of MAOA in AD include dinucleotide and premotor polymorphisms. In case-control postmortem studies, increases in the activities of MAOA, MAOB, or both have been reported in AD, while regional declines in monoamine transmitters, precursors, or metabolites have been reported in the prefrontal [11], frontal pole [12], and caudate regions [13–15]. In controls, the high activity genotype group has shown greater dopamine turnover in cerebral spinal fluid [2]. In addition, for *MAOA-VNTR* genotype groups, patients with AD associated with the high activity genotype have shown higher brain MAOA activity and gene expression than controls [5]. Although in AD the expression of the MAOA gene and regional levels are in the same direction, controversy exists with regard to alcoholics, as the low activity group may show higher monoamine metabolites levels [2]. The inconsistencies in the findings suggest the complexity of genotype or epigenetic effects [16] in different disease spectrums.

Recent research has suggested that regions that are highly related may show covariance in morphometric characteristics, so-called structural covariance network (SCN). The striatum subserves a wide range of high cortical functions, and researchers have conceptualized the functional circuits associated with six striatal sub-regions [17]. The use of SCNs as endophenotypic measures in genetic studies is potentially advantageous, since network patterns provide insights into symptom prediction. The default mode network [18], salience network [19], and executive control network [18, 20] are of clinical relevance in AD, collectively termed the triple-network model [21]. The striatal SCN [17] and triple-network SCN may represent ideal models to understand the modulation of *MAOA-VNTR* genotypes with regard to the cognitive features.

This study explored the topography of brain networks mediated by *MAOA-VNTR* genotypes. Although the classification of MAOA-VNTR transcriptional efficiency into three functional groups has been well established [4], the lack of male sex in the LH group makes this functional group unique when analyzing genetic influences on the brain network. A difference has been found between female alcoholics with reported aggressiveness and social complications, with a significantly larger proportion of individuals carrying at least one MAOA-VNTR high activity allele [7]. As such, our group stratification was made in hemizygous males with 3 or 4 repeats, homozygous females with 3 repeats, and females with 4 repeats (LH + H) using a 2 × 2 mixed factorial design model. As the caudate and prefrontal axes represent regions showing lower monoamine levels in AD [22, 23], we hypothesized that the higher activity MAOA-VNTR genotype group may be associated with stronger prefrontal-caudate network covariance strength, and that such a degenerative network may represent endophenotypes to predict neurobehavioral performance. The rationale of this hypothesis was based on postmortem data in AD that MAOA activity may be upregulated selectively in the prefrontal-caudate axis [11, 13, 14] and in those with the high activity genotype group of the functional MAOA-VNTR polymorphism showing greatest transcriptional efficiency [4].

Materials and 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 Department of General Neurology, Kaohsiung Chang Gung Memorial Hospital. AD was diagnosed according to the International Working Group criteria [24] with a clinical diagnosis of typical AD [25]. A total of 193 subjects (99 males, 94 females) were included into this study, all of whom were in a stable condition under acetylcholine esterase inhibitor treatment. The exclusion criteria were a modified Hachinski ischemic score > 4, territorial stroke,

negative amyloid scan by visual interpretation, and premorbid major depressive disorders.

Study Working Scheme

The SCNs were established by seed-based correlation analysis (Fig. 1A and supplementary Fig. 1). The functional genotype groups [6] were as follows: Low activity group (L group): men = 2 repeats, 3 repeats, and 5 repeats; women = 2/2, 3/3, 5/5, 2/3, 2/5, and 3/5; Low-High group (LH group): women = 2/4, 2/3.5, 3/4, 3/3.5, 5/4, 5/3.5; and High activity group (H group): men = 4 repeats and 3.5 repeats; women = 3.5/3.5, 4/4, and 4/3.5.

The main effects of genotype, sex, or their interactions were then entered into the general linear model to predict the seed regional volumes. Only the aforementioned significant seeds were selected for next-step covariance strength analysis (Fig. 1B). As female sex had three genotype groups, the network interactions exploring the independent effects of sex, genotype, or sex-genotype group interactions in the female group were analyzed by pooling the LH and H groups as one group (LH + H group). Specific t contrast for the genotype specific covariance strength effects was modeled using H > L group (in males) or LH + H > L group (in females). Sex-genotype group interactions were modeled using univariate analysis of variance (factor 1: MAOA-uVNTR genotype group, factor 2: sex [male, female]). The volumes of the significant peak clusters were reported and correlated with neurobehavioral scores to understand the clinical relevance (Fig. 1C).

(For descriptions of the neurobehavioral tests, *MAOA*-VNTR genotyping, and image acquisition, see online supplementary file 1.)

Data Analysis for Neuroimaging Biomarkers

Image preprocessing and statistical analysis were performed using SPM12 (SPM12, Wellcome Trust Centre of Cognitive

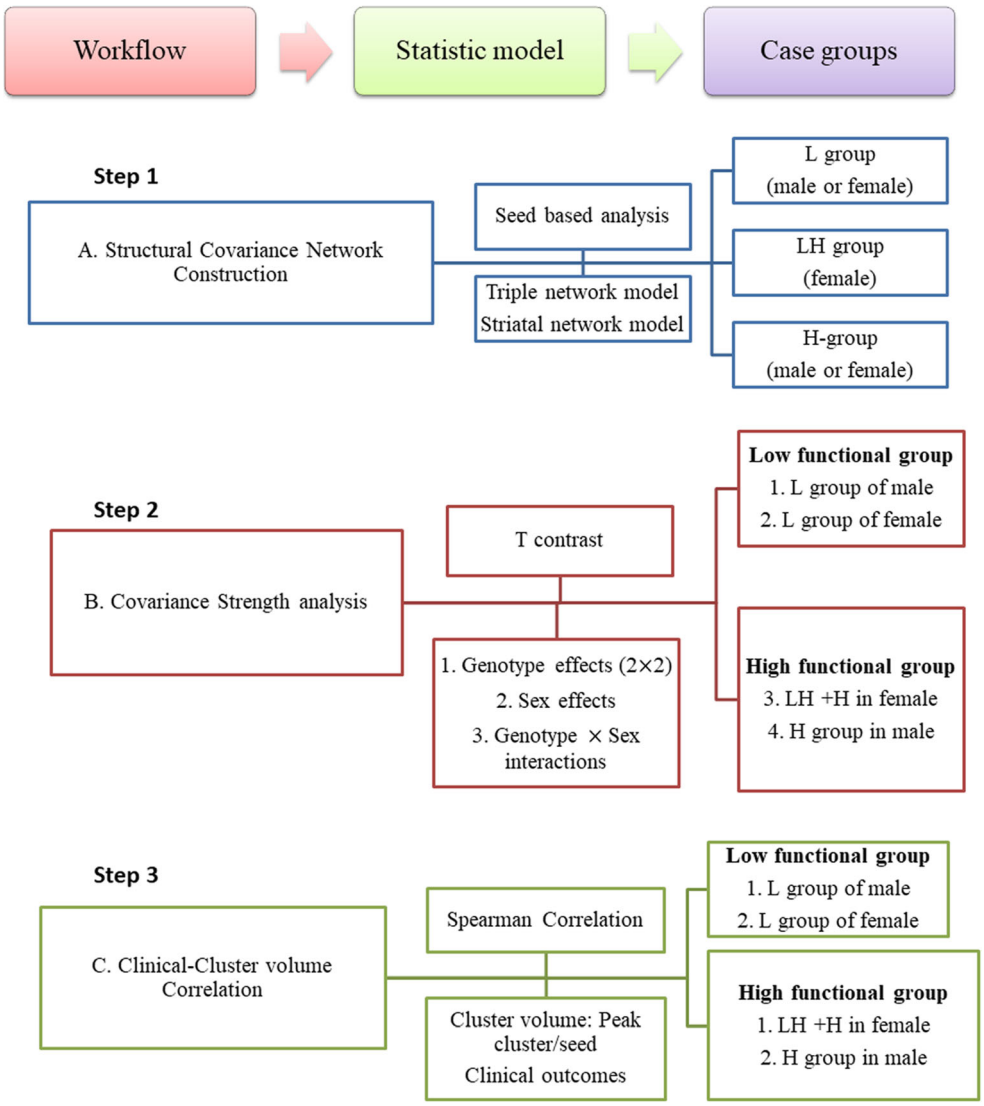

Fig. 1 Working scheme of the study. Low activity [L] group, $n = 87$; low-high activity [LH] group, $n = 41$; high activity [H] group, $n = 65$. The groups were stratified by the monoamine oxidase A variable number of tandem repeats

Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/). T1 images were reoriented, realigned, and normalized using the standard Montreal Neurological Institute space. The images were then segmented into GM partitions. Related tissue segments were used to create a custom template using diffeomorphic anatomical registration with the exponentiated lie algebra approach. The modulated and warped images were then smoothed using a Gaussian kernel of 8 mm full width at half maximum.

Images Analysis

To investigate the SCNs, nine seed regions of interest were selected from the preprocessed images. The striatal network [17] included the following six seeds: inferior ventral striatum coordinates = (9,9,− 8), ventral striatum superior (VSs) coordinates = (10,15,0), dorsal caudate (DC) coordinates = (13,15,9), ventral rostral putamen coordinates = (20,12,− 3), dorsal caudal putamen coordinates = (28,1,3), dorsal rostral putamen coordinates = (25,8,6). The coordinates of seeds in the triple-network model included the left posterior cingulate cortex coordinates = (− 2,− 36, 35) of the default mode network, right frontoinsular cortex coordinates = (38, 26,− 10) of the salience network, and right dorsolateral prefrontal cortex (dLPFC) coordinates = (44,36,20) of the executive control network [19].

Statistical Analysis

Clinical and laboratory data were expressed as mean ± standard deviation. One-way analysis of variance with Bonferroni correction was used, as appropriate, to compare continuous variables. The chi-square test was used to compare categorical variables. Spearman correlation analysis was used to analyze the seed or cluster volume on predicting the cognitive or NPI scores. The sex and genotype group effects on the seed volume or the interactions were calculated using the general linear model. All statistical analyses were conducted using SPSS software (SPSS version 20.0 for Windows®, SPSS Inc., Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

Demographic Data, Neurobehavior Data, and SCN

There were no 2, 5, or 3.5R carriers in the patient pool (Table 1). Genotype distribution within the female sample did not deviate significantly from Hardy-Weinberg equilibrium (chi-square = 1.255; $p = 0.26$). Due to hemizygosity in the male subjects, no Hardy-Weinberg equilibrium could be calculated. There was no significant difference in allele frequencies between sexes (chi-square = 0.0023, $p = 0.96$).

Table 1 *MAOA*-VNTR functional genotype groups

Genotype	Percent	Numbers
Female		
3/3 (low activity group)	34.04	32
3/4 (low-high activity group)	43.62	41
4/4 (high activity group)	22.34	21
3-repeats allele	55.85	105
4-repeats allele	44.15	83
Male (hemizygote)		
3-repeats (low activity group)	55.56	55
4-repeats (high activity group)	44.44	44

MAOA-VNTR monoamine oxidase, isozyme A, variable number of tandem repeats

In comparisons of demographic data and cognitive test scores, there were no significant differences in sex, age, ApoE4 status, and educational level among the two genotype groups (Table 2) or three genotype groups (Supplementary Table 1). As the number of cases was more balanced in each group, the qualitative display among three functional groups may have helped to understand whether there was a dose-dependent effect and balance of the statistical significance in the SCN distributions. The SCN maps of the three genotype groups are shown in Supplementary Fig. 1, and the significant clusters and the coordinates are shown in Supplementary Table 2–28.

Genotype, Sex, or Interaction in the Seed Volumes

After pooling the female LH and H groups, we explored whether sex affected the predefined seed volumes in the MAOA genotype groups. There were significantly larger seed volumes in the female LH + H group compared with the male H group in the dLPFC and DC (Table 3). These differences in volume were driven by the interaction of sex. An interaction of sex and genotype was also seen in the VSs seed; however, the volume of either the female LH + H or female L group only reached borderline significance with the male L group.

Seed Volumes and Clinical Correlations

As the dLPFC seed volumes showed interactions with sex, the genotype effect and clinical significance of each seed volume were further established by correlating them with neurobehavior test scores, stratified by the 2 ×2 groups (Table 4). As short-term memory test scores are salient features of AD, the significance was established in dLPFC, DC, and VSs seed volumes in the female LH + H group and the male L group. In comparisons, correlations between seed volume and neuropsychiatric inventory scores were less significant.

Table 2 Cognitive test scores in two genotype groups

Group	L group	LH + H group
Male/female	55/32	44/62
Age, year	73.4 (7.7)	73.7 (8.2)
Education, year	7.9 (4.8)	6.9 (4.9)
Apolipoprotein E4 carrier (positive case, %)	34 (39.1%)	38 (35.8)
Mini-Mental State Examination	20.0 (6.8)	19.8 (6.4)
CASI total scores	66.9 (23.1)	65.9 (20.5)
CASI Executive Function Test scores	24.8 (8.9)	24.3 (7.7)
CASI subdomains		
Short-term memory	5.3 (4.0)	5.3 (3.7)
Orientation	12.6 (5.1)	12.6 (5.4)
Long-term memory	8.3 (2.9)	7.9 (2.7)
Language	8.1 (2.5)	8.1 (2.1)
Drawing	7.7 (2.9)	7.8 (2.8)
Attention	6.1 (1.7)	6.2 (1.5)
Verbal fluency	5.4 (3.0)	4.6 (2.5)
Abstract thinking	8.1 (2.9)	8.1 (2.7)
Mental manipulation	5.3 (3.1)	5.4 (3.4)
Neuropsychiatric inventory total scores	8.0 (11.6)	8.3 (11.8)

Data are presented as mean (standard deviation) or number (percentage; %)

CASI, Cognitive Ability Screening Instrument, attention, verbal fluency, abstract thinking, and mental manipulation sub-domain scores of the CASI were added to assess executive function; *L group*, low activity group; *LH + H group*, low-high + high activity groups; *MAOA-VNTR*, monoamine oxidase, isozyme A, variable number of tandem repeats; APOE4 carriers were defined as the presence of one or two APOE4 alleles

Table 3 Comparisons of seed volumes in three *MAOA*-VNTR genotype groups and two gender groups

Volumes Coordinate	PCC (− 2,− 36,35)	FI (38,26,− 10)	dLPFC (44,36,20)	VSi (9,9,− 8)	VSs (10,15,0)	DC (13,15,9)	DCP (28,1,3)	DRP (25,8,6)	VRP (29,12,− 3)
3 functional genotype groups									
L group	0.61 (0.13)	0.55 (0.14)	0.44 (0.12)	0.62 (0.15)	0.66 (0.27)	0.79 (0.33)	0.63 (0.27)	0.68 (0.27)	0.61 (0.31)
LH group	0.63 (0.11)	0.53 (0.15)	*0.47 (0.10)*	0.66 (0.15)	*0.72 (0.21)*	*0.88 (0.28)*	0.66 (0.25)	0.74 (0.25)	0.66 (0.28)
H group	0.61 (0.10)	0.51 (0.15)	*0.42 (0.13)**	0.64 (0.16)	*0.61 (0.32)**	*0.71 (0.32)***	0.59 (0.32)	0.65 (0.32)	0.56 (0.32)
Genotype, sex 2 ×× 2 model									
Female									
L group	0.61 (0.12)	0.59 (0.16)	0.45 (0.10)	0.67 (0.13)	0.72 (0.21)	*0.88 (0.33) **	0.66 (0.24)	0.71 (0.26)	0.63 (0.28)
LH + H group	0.62 (0.11)	0.52 (0.15)	*0.47 (0.11)**	0.65 (0.16)	0.71 (0.26)	*0.85 (0.32) **	0.65 (0.27)	0.72 (0.28)	0.64 (0.29)
Male									
L group	0.60 (0.13)	0.53 (0.13)	0.43 (0.13)	0.60 (0.15)	0.63 (0.30)	0.73 (0.32)	0.61 (0.29)	0.66 (0.27)	0.60 (0.32)
H group	0.61 (0.10)	0.52 (0.14)	0.39 (0.13)	0.65 (0.15)	0.57 (0.30)	0.68 (0.29)	0.58 (0.31)	0.63 (0.32)	0.55 (0.32)
Genotype-sex interaction (linear regression model)									
Genotype	0.108 (0.898)	2.505 (0.084)	0.208 (0.812)	0.121 (0.886)	0.345 (0.708)	1.176 (0.311)	0.418 (0.659)	0.316 (0.729)	0.466 (0.628)
Sex	0.380 (0.539)	0.254 (0.615)	*5.064 (0.026)*	1.458 (0.229)	*5.009 (0.026)*	*5.126 (0.025)*	0.712 (0.400)	1.357 (0.246)	0.592 (0.443)
Interactions	0.002 (0.964)	3.381 (0.068)	3.046 (0.083)	2.149 (0.144)	0.127 (0.722)	0.188 (0.665)	0.002 (0.963)	0.002 (0.968)	0.011 (0.918)

Data presented in the L-group and H-group columns are mean (standard deviation) of seed volumes. Data presented in the Genotype × Sex interaction columns as *F* value (*p* value). The Italic emphasis indicates statistical significance between LH group and H group

L group low activity group, *LH group* low-high activity group, *H group* high activity group, *PCC* posterior cingulate cortex, *FI* frontoinsular, *dLPFC* dorsolateral prefrontal cortex, *VSi* inferior ventral striatum, *VSs* superior ventral striatum, *DC* dorsal caudate, *DCP* dorsal caudal putamen, *DRP* dorsal rostral putamen, *VRP* ventral rostral putamen, *MAOA-VNTR* monoamine oxidase, isozyme A, variable number of tandem repeats

$^{*}p < 0.05$; $^{**}p < 0.01$ compare with H group in male

Table 4 Relationships between seed volumes and neurobehavior scores

Seed region	Right dorsolateral prefrontal cortex				Right ventral striatum superior				Right dorsal caudate			
	Woman		Man		Woman		Man		Woman		Man	
MAOA-uVNTR groups	L	LH + H	L	H	L	LH + H	L	H	L	LH + H	L	H
Mini-Mental State Examination	− 0.203	0.243	*0.352***	*0.391***	0.089	*0.428***	0.228	*0.370**	− 0.058	*0.330***	0.018	*0.553***
CASI total scores	− 0.249	0.124	*0.382***	*0.303**	0.115	*0.445***	0.247	*0.336**	− 0.022	*0.290**	0.021	*0.415***
CASI EFT scores	− 0.330	− 0.107	*0.424***	0.262	0.194	*0.362***	0.244	0.278	− 0.020	0.206	0.027	*0.430***
Short-term memory	− 0.163	*0.259**	*0.403***	0.179	− 0.112	*0.365***	0.163	0.279	− 0.295	*0.269**	0.059	0.182
Orientation	− 0.213	0.244	0.187	0.286	0.001	*0.382***	0.136	0.277	− 0.027	*0.253**	− 0.058	*0.358***
Long-term memory	− 0.216	0.115	*0.273**	0.238	0.340	*0.390***	*0.344**	0.130	0.146	*0.333***	0.057	0.254
Language	− 0.078	0.115	*0.279**	0.294	0.168	0.245	*0.506***	0.171	0.096	0.240	0.291	*0.363**
Drawing	− 0.177	− 0.126	0.179	− 0.027	0.262	0.201	0.116	0.017	0.195	*0.250**	− 0.050	0.159
Attention	− 0.178	0.004	*0.359***	0.203	0.300	*0.281**	*0.209**	0.232	− 0.002	0.092	0.021	0.282
Verbal fluency	− 0.291	− 0.012	*0.355***	0.261	0.162	*0.454***	*0.314**	0.235	0.114	0.208	0.121	0.243
Abstract thinking	*− 0.408**	− 0.094	*0.374***	0.164	0.155	0.162	0.301	− 0.047	− 0.078	0.048	0.134	0.185
Mental manipulation	− 0.249	− 0.087	0.250	0.134	0.139	0.238	− 0.010	*0.331**	− 0.056	0.199	− 0.169	*0.523***
NPI total scores	0.258	0.011	0.020	0.150	− 0.035	− 0.093	0.074	0.021	− 0.059	− 0.098	*0.290**	0.077
Delusion	0.080	− 0.119	0.014	0.012	0.005	− 0.110	− 0.209	0.015	0.002	− 0.095	0.015	0.023
Hallucination	0.101	0.021	− 0.175	− 0.210	− 0.119	− 0.096	− 0.212	− 0.222	− 0.228	− 0.238	− 0.181	− 0.234
Aggression	0.243	0.078	0.176	− 0.183	− 0.088	− 0.041	0.082	− 0.141	− 0.126	0.013	0.009	− 0.115
Depression	0.339	0.074	0.059	0.158	0.110	− 0.115	0.063	0.016	0.105	0.002	0.187	− 0.062
Anxiety	0.007	− 0.146	− 0.013	0.227	0.183	− 0.172	− 0.125	− 0.024	0.034	− 0.131	− 0.138	0.054
Elation	0	− 0.068	− 0.017	− 0.198	0	− 0.140	− 0.197	− 0.198	0	− 0.147	− 0.051	− 0.036
Apathy	0.005	− 0.033	− 0.177	− 0.246	0.290	− 0.188	− 0.052	− 0.167	0.087	− 0.182	0.119	− 0.134
Disinhibition	− 0.165	− 0.136	− 0.025	0.082	0.146	0.017	*− 0.281**	0.160	0.117	− 0.017	− 0.002	0.071
Irritability	0.184	0.141	0.012	0.158	0.280	0.124	− 0.097	0.055	0.075	− 0.007	0.022	0.037
Aberrant motor behavior	0	− 0.072	− 0.136	− 0.174	0	− 0.093	− 0.100	− 0.083	0	− 0.167	− 0.024	− 0.042
Sleep	− 0.203	0.016	0.203	0.197	*− 0.583**	0.155	0.155	− 0.010	− 0.307	0.105	*0.294**	0.093
Eating disorder	− 0.083	0.078	− 0.022	− 0.257	0.030	− 0.160	− 0.072	0.159	− 0.040	− 0.065	− 0.072	− 0.098

The Italic emphasis indicate statistical significance

CASI Cognitive Ability Screening Instrument, *EFT* Executive Function Test, *NPI* Neuropsychiatric Inventory, *L group* low activity group, *LH group* low-high activity group, *H group* high activity group, *LH + H group in woman* high activity+ low-high activity group, *MAOA-VNTR* monoamine oxidase, isozyme A, variable number of tandem repeat

Numbers indicate correlation coefficient, $*p < 0.05$; $**p < 0.01$

Interactions of Structural Covariance Strength According to Genotype, Sex, or Interactions

We further tested the independent roles of genotype, sex, or their interactions in structural covariance strength.

Main Effect of Genotype Groups

To test the effects of the genotype, we analyzed areas sharing identical clusters in the males and females. Only the dLPFC anchoring the caudate region showed an independent effect. However, the relationships of covariance strength in genotype groups were different between the females (H + LH < L group) and males (H > L group) (Fig. 2a).

Interactions Between Sex-Genotype Groups

Covariance strength showing sex and genotype interactions was seen in the dLPFC-anchored supplementary motor area (SMA) network (Fig. 2b), DC anchored the precentral network and SMA network (Fig. 2c). The covariance strength was higher in the female L group and the male H group.

Main Effects of Sex Groups

The main effects of sex were seen in the three peak clusters in the dLPFC, DC, and VSs seeds (Fig. 3). For the sex effect showing covariance strength interactions (male group > female group), interactions were seen in the frontal

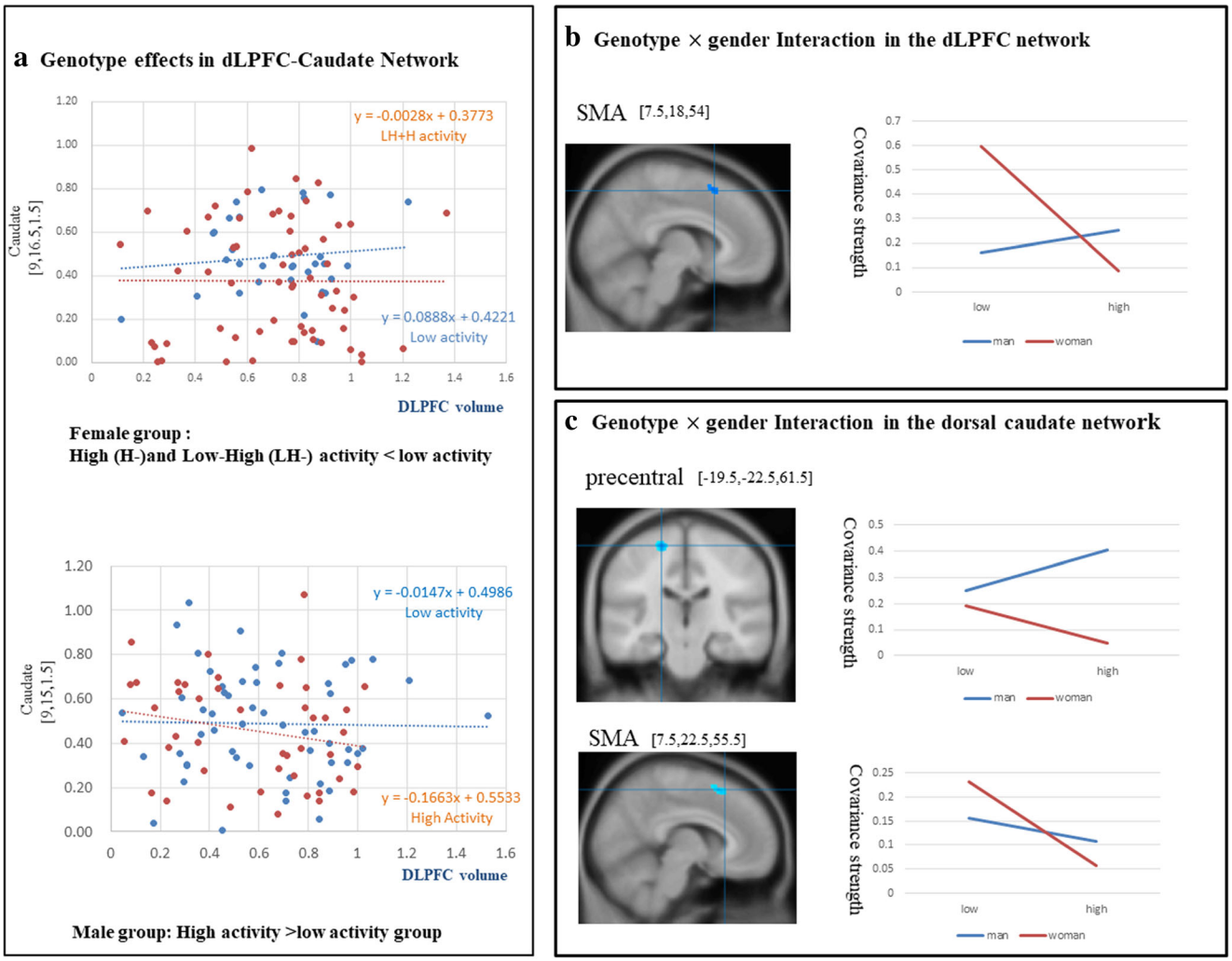

Fig. 2 Genotype effects showing significant differences in covariance strength of monoamine oxidase A variable number of tandem repeat groups stratified by sex (**a**) or interaction with sex (**b**, **c**). dLPFC = dorsal lateral prefrontal cortex; SMA = supplementary motor area. (x,y,z) = Montreal Neurological Institute coordinates. Statistical threshold corrected with false discovery rate (FDR) at $p < 0.01$ and cluster size > 100 voxels

medial superior and lingual cluster anchored by dLPFC. The peak clusters of frontal operculum consistently showed higher covariance strength in the female group in the dLPFC-, VSs-, and DC-anchored networks. In the DC- and VSs-anchored networks, the female group showed higher covariance strength in the lingual peak clusters.

Clinical Significance of Peak Cluster Volumes

The three peak cluster volumes in each network were extracted and correlated with cognitive test scores (Table 5). The lingual volume predicted test scores in the male group, while the frontal operculum region volume predicted short-term memory, orientation, and drawing scores in the female group.

Discussion

Major Findings

This study explored the effects of *MAOA-VNTR* genotypes, sex, and interactions on the influence of SCNs, and explored the clinical significance in patients with AD. There were three major findings. First, the topography of covariance strength interactions suggested an important weighting of executive control network in mediating the MAOA-VNTR genotype networks. The independent effect of the MAOA-VNTR polymorphism was found to modulate the covariance strength on the caudate-dLPFC axis, of which the DC and dLPFC volumes correlated significantly with the salient short-term memory scores. Interestingly, the *MAOA-VNTR* genotype in the dLPFC-caudate axis

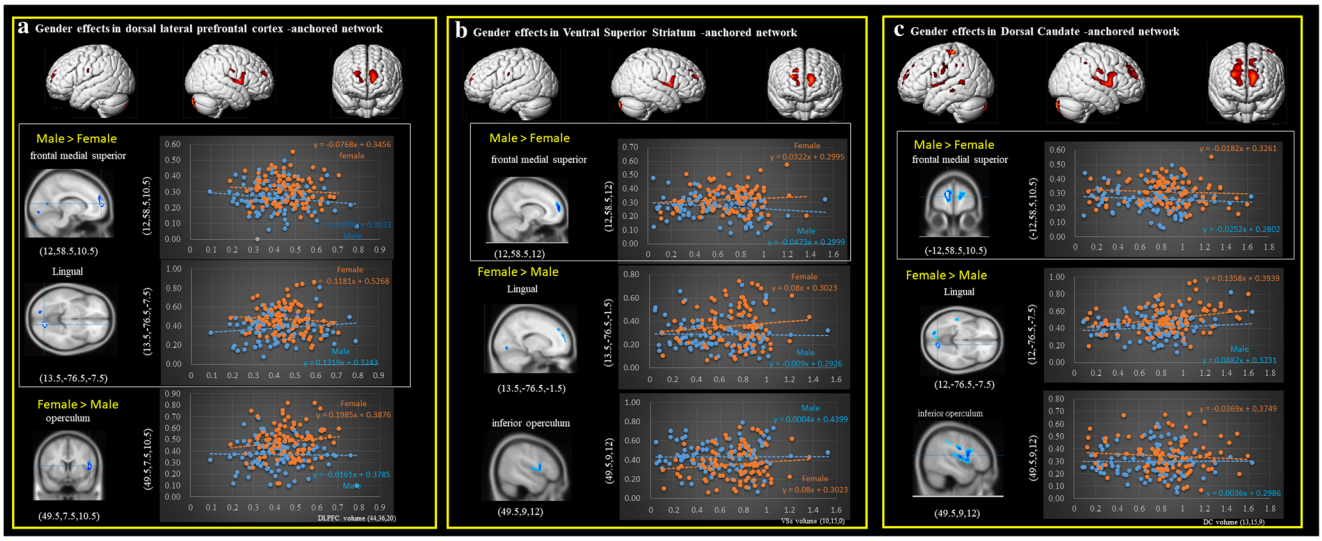

Fig. 3 Peak clusters showing significant interactions of monoamine oxidase A variable number of tandem repeat groups: from the **a** dorsal lateral prefrontal cortex (dLPFC), **b** ventral superior striatum (VSs) seed, and **c** dorsal caudate (DC) seed. (x,y,z) = Montreal Neurological Institute coordinates. Statistical threshold corrected with false discovery rate (FDR) at $p < 0.01$ and cluster size > 100 voxels

showed an opposite effect on covariance in the female and male groups. Second, the regression model suggested interactions between sex and MAOA-VNTR genotype in the dLPFC-SMA, DC-precentral, and DC-SMA axes, all located in the anterior brain region. This result showed the significance of the prefrontal-dorsal striatum, while the differences in covariance strength may provide a possible mechanism to understand those at risk in the two sexes. Lastly, peak clusters showing greater covariance strength in the male or female groups were localized in close anatomical sites in the three predefined seed-anchored networks, pointing to the importance of medial frontal, frontal operculum, and lingual regions. As the clinical correlations of the peak clusters also explained the cognitive test scores, the results show network modulation by sex and genotype in AD cognitive performance.

Methodological Considerations on the Interactions of Sex and MAOA-VNTR Functional Genotypes

Based on the biological nature of the *MAOA* gene, males are genetically hemizygous and females are functionally hemizygous due to random X-inactivation [26]. The inhomogeneity of heterozygous females in the LH group and the X-inactivation in the monozygous females suggest differences in enzymatic activity compared with the hemizygous males. In fact, the sex interaction effect was seen in our cognitive comparisons showing higher verbal fluency scores in the L group (supplementary Table 1). Similarly, differences in seed volumes in the dLPFC, VSs, and DC between the LH group and H group also demonstrated a significant sex effect (Table 3).

Direct stratification of the inherited *MAOA* genotype groups without testing interactions between sex and genotype groups may not fully address the influence of sex- or sexual hormone-mediated genetic expressions of MAOA [27]. In transfected cell line, MAOA activity has been shown to be reduced by treatment with estrogen [28], while testosterone in male subjects has been shown to modulate their behavior even in the low activity group [29]. The enrollment of a 3R/4R group should consider random X-inactivation, functional expression of MAOA, and the influence of estrogen related to the sex effects. Such group stratification may help to delineate the factors related to genotype or sex on the brain network scaffold; however, individual differences in X-inactivation in females and the expression confounded by hormones still could not be explained.

MAOA Genotype Effects in the dLPFC-Caudate Axis

The caudate region anchored by the dLPFC seed represented the only identical region in both sexes. Covariance strength analysis suggested differences in sex-related genotype effects in seed-peak cluster covariance strength, so the MAOA-VNTR genotype targeting this particular axis in female and male patients should be considered as different mechanisms. We previously reported that stronger covariance strength between seed and peak clusters indicates more intra-network connections [30]. Alternatively, the decrease in covariance strength may imply disconnections or changes in compensatory mechanisms that were independent of the degenerative processes. Our results indicate that the male H activity or female L groups may be considered to be at risk of dLPFC- or DC-anchored network degeneration. However, further longitudinal studies are needed to elucidate whether "more intra-network connections" indicate faster degenerative processes.

Table 5 Peak cluster volume and cognitive test scores correlations

Peak cluster region	Medial superior frontal		Lingual		Frontal operculum	
Dorsolateral prefrontal cortex network						
Coordinate	[12,58.5,10.5]		[13.5,− 76.5,− 7.5]		[49.5,7.5,10.5]	
Covariance strength	Male > female		Male > female		Female > male	
	Male	Female	Male	Female	Male	Female
MMSE	− 0.024	0.033	*0.206**	0.027	0.021	− 0.135
CASI total scores	− 0.005	0.025	*0.234**	− 0.002	− 0.036	− 0.089
CASI EFT scores	0.012	− 0.025	*0.224**	0.042	− 0.096	0.010
Short-term memory	0.005	0.049	0.161	0.028	− 0.037	*− 0.208**
Orientation	0.012	0.049	*0.285***	0.066	0.083	*− 0.237**
Long-term memory	0.057	0.015	0.088	− 0.044	0.013	− 0.032
Language	− 0.047	− 0.019	0.191	− 0.124	0.009	− 0.054
Drawing	− 0.093	− 0.005	0.152	− 0.063	− 0.085	0.112
Attention	0.098	0.087	0.106	0.014	0.040	− 0.066
Verbal fluency	− 0.060	0.010	*0.242**	0.023	− 0.097	− 0.117
Abstract thinking	0.006	− 0.104	0.149	0.015	− 0.031	0.061
Mental manipulation	0.031	− 0.016	0.195	0.060	− 0.170	0.082
Ventral superior striatum network						
Coordinate	[12,58.5,12]		[13.5,− 76.5,− 1.5]		[49.5,9,12]	
Covariance strength	Male > female		Female > male		Female > male	
	Male	Female	Male	Female	Male	Female
MMSE	0.069	− 0.017	0.024	0.004	− 0.013	− 0.171
CASI total scores	0.073	− 0.036	0.045	− 0.012	− 0.037	− 0.127
CASI EFT scores	0.053	− 0.050	0.030	0.056	− 0.084	− 0.033
Short-term memory	0.149	0.063	0.174	− 0.019	− 0.058	*− 0.246**
Orientation	0.108	− 0.025	− 0.016	− 0.019	0.057	*− 0.261**
Long-term memory	− 0.042	− 0.100	− 0.034	− 0.011	0.036	− 0.048
Language	0.057	− 0.024	0.002	− 0.058	0.019	− 0.059
Drawing	− 0.018	− 0.089	0.048	− 0.079	− 0.078	0.064
Attention	0.050	0.101	− 0.013	− 0.002	0.012	− 0.112
Verbal fluency	− 0.005	− 0.084	− 0.082	0.032	− 0.067	− 0.143
Abstract thinking	− 0.003	− 0.096	0.093	0.001	− 0.005	0.039
Mental manipulation	0.128	− 0.016	0.084	0.104	− 0.173	0.039
Dorsal caudate network						
Coordinate	[− 12,58.5,10.5]		[12,− 76.5,− 7.5]		[49.5,9,12]	
Covariance strength	Male > female		Male > female		Female > male	
	Male	Female	Male	Female	Male	Female
MMSE	0.047	− 0.012	0.040	− 0.007	0.103	0.013
CASI total scores	0.038	− 0.049	0.069	− 0.051	0.105	0.037
CASI EFT scores	0.007	− 0.057	0.059	− 0.039	0.047	0.132
Short-term memory	0.102	0.045	0.073	− 0.010	0.053	− 0.131
Orientation	0.083	− 0.066	0.059	0.002	0.113	− 0.110
Long-term memory	− 0.025	− 0.111	− 0.007	− 0.076	0.155	0.041
Language	0.041	0.002	0.058	− 0.008	0.076	− 0.057
Drawing	− 0.030	− 0.061	0.079	− 0.108	*0.204**	*0.253**
Attention	0.033	0.086	0.019	− 0.106	0.113	0.011
Verbal fluency	− 0.077	− 0.108	0.020	− 0.115	− 0.037	0.050
Abstract thinking	− 0.030	− 0.121	0.097	− 0.077	0.035	0.152
Mental manipulation	0.104	0.011	0.042	0.097	0.071	0.138

The Italic emphasis indicate statistical significance

Selected peak clusters indicate structural covariance strength showing high activity group > low activity group

MMSE Mini-Mental State Examination, *CASI* Cognitive Ability Screening Instrument, *EFT* Executive Function Test, *SMA* supplementary motor area, *MAOA-VNTR* monoamine oxidase, isozyme A, variable number of tandem repeats

Numbers indicate Pearson correlation coefficients, $^{*}p < 0.05$

In AD, MAOA activity has been reported to be higher in H groups, [5] so the SCN patterns and covariance strength may have reflected associations of MAOA activity in the seed-anchored covariance network. Direct inspection of the SCN topographic maps among the three *MAOA* genotype groups did not suggest such an association. The pair-wise correlations between seed and peak cluster volume also did not support a relationship between MAOA activity and SCN topography, as shown by the genotype effects in both sexes. According to studies using [^{11}C] clorgyline positron emission tomography (PET) quantification, brain MAOA activity does not correspond to the MAOA-VNTR "high" and "low" alleles in healthy male subjects [31]. In contrast, the methylation state of the MAOA gene has been shown to be associated with the

endophenotype [16]. In AD, the disease-related upregulation of MAOA activity should also be taken into consideration [5], and the expressions were not parallel to the healthy controls.

dLPFC and DC Networks with Genotype-Sex Interaction

Covariance strength analysis suggested genotype-sex interactions in the dLPFC and DC networks, implying the joint effects on the anterior brain axis. Sex-related effects on *MAOA* genotypes have been reported to affect the behavior traits or brain morphometrics in male and female subjects. However, studies on genetic-sex interactions and behavior traits have reported inconsistent findings. In males, either L activity [32, 33] or H activity [34, 35] has been reported to be correlated with more aggressive behavior. Similarly in female subjects, both the high activity *MAOA* genotype [36–38] and low activity homozygous female AD carriers have been reported to show significant depressive symptoms [39]. In our study, the female L group and the male H group had greater weighting showing covariance strength interactions in the DC- or dLPFC-anchored networks. While the covariance relationships were parallel with the genotype main effects, the differences in covariance strength between the males and females suggested sex-related genotype modulations in these networks.

As the cortical hubs of the striatum networks are highly functionally anchored, spatially scattered caudate-related SCN clusters may imply the role of *MAOA-VNTR* polymorphisms in the functional pathways. In normal participants with the MAOA-VNTR 4R genotype, greater brain activities were found in the insula, middle frontal, superior and inferior temporal regions compared with the 3R genotype group, indicating that these regions may participate in the genetic expressions [40].

Stronger correlations modulated by increased MAOA activity may suggest greater regional connectivity and synchronized GM loss in regions targeted by pathological process. As the strength of structural covariance represents collinearity between seed and peak cluster volumes, topographies showing higher covariance strength in the male H group or female L group indicated stronger degenerative dynamics between seed and peak clusters. Normal males aged 20–47 with the MAOA-H genotype have been shown to have decreased GM volumes in bilateral orbitofrontal regions [41], suggesting that the influence of this genotype may begin in the developmental phase. The topographic similarities in our AD patients and controls suggest that common pathways are modulated by MAOA.

Sex Effects on dLPFC-, VSs-, or DC-Cortical Degeneration

Our study explored the independent role of sex on SCN. The covariance strength analysis suggested how sex may mediate the structural connectivity in the dLPFC-, VSs-, or DC-cortical axis in AD. The male patients consistently showed higher covariance strength in the frontal medial superior region compared to the operculum areas in the female patients. Differences in peak lingual clusters in the executive control network and striatal network support that functional networks may be modulated by sex. The sex-related changes in structural covariance may reflect the complex relationships of developmental, degeneration, or epigenetic factors.

Role of *MAOA* Genotypes in AD Neurobehavior Changes

In healthy subjects, MAOA-VNTR genotype groups have been linked with attentional networks [42]. We demonstrated the clinical significance of dLPFC, VSs, and DC seeds or peak clusters with related cognitive function (Tables 4 and 5). The significant correlations between cognitive outcomes and seed (or peak cluster) volumes may help to address the pathological-genetic alterations of local clustering.

In healthy subjects, MAOA-VNTR genotype groups have been linked with the harm avoidance personality trait [43]. The association between ventral striatum MAOA level and striatal functional connectivity may be linked to impulsive behavior in subjects with antisocial personality disorder [44]. Other studies with male patients have suggested an increase in antisocial personality trait or aggression with the low-expression *MAOA* genotype [45, 46]. Our network morphometric data support the genotype effects and behavior changes in AD, as some of the neuropsychiatric presentations were related to VSs or DC volumes. However, the behavior changes in AD were less related to the *MAOA* genotypes compared with the cognitive test correlations.

Study Limitations

The stratification of the patients according to the *MAOA* genotype and sex may have led to inconsistencies in data interpretation. Based on the literature, the analysis of MAOA-VNTR genetic effects considering sex and *MAOA* genotype group factors can be managed in two major ways. To minimize the sex effect, some studies have explored the genetic effects by enrolling only one sex [2, 42, 43, 47]. However, this may limit the application of the study results to the opposite sex. Others studies have explored genotype, sex effects, and their interactions on outcome measures. While the independent role of sex [48] or interactions of both factors [39] can be analyzed, inconsistent trends in sex and genotype effects may have been related to inhomogeneous samples in allele frequency and genotype case numbers. The analysis still could not control for variances in hormonal effects or X-inactivation. Our study design treated the LH and H groups of females as one genotype group, and we found coherent clusters in both sexes. With such stratification, the number of cases in the

LH + H group still outweighed the L group in the females, so the spatial extent of SCN in the LH + H group would be more extensive than that in the L group. To avoid confusion over the qualitative display, we reported the SCN maps stratified by three functional groups. Second, as the clinical significance was established in the predefined networks, our study design was not able to test whether other networks may participate in MAOA genetic modulation. Nonetheless, the results were consistent with the literature in that the prefrontal-striatal network played a major role in the expression of MAOA [11, 13–15]. The use of independent component analysis [49] or resting state functional MRI data may help to elucidate other potential networks and validate the findings observed here.

Conclusions

Using SCN and covariance strength analysis, this study identified independent roles of *MAOA* genotype, sex, and their interactions in the degenerative scaffolds in the early stages of AD. Via sex or interactions with sex, the MAOA-VNTR polymorphism appears to target the executive control and dorsal striatum networks. The higher covariance strength in the caudate-prefrontal axis of the male H group and female L group emphasizes the differences in MAOA genotype effects between sexes.

Acknowledgements The authors wish to thank the patients and their caregivers for their time and commitment to this research.

Author's Contribution Chiung-Chih Chang and Shih-Jen Tsai conceived and designed the research; Ya-Ting Chang, Chi-Wei Huang, and Shih-Wei Hsu performed the experiments and Hsin-I Chang analyzed the data; Mu-En Liu, Wen-Neng Chang, Chia-Yi Lien, Shu-Hua Huang, and Chen-Chang Lee provided technical support; Chiung-Chih Chang drafted the initial manuscript; Hsin-I Chang, Chiung-Chih Chang, and Shih-Jen Tsai edited and revised the manuscript.

Funding This work was supported by grants CMRPG8C0571, CMRPG8D0771, CMRPG8G1521, and CMRPG8E0541 from Chang Gung Memorial Hospital, and 104-2314-B-182A-026-MY2 from the National Science Council to CCC for MRI acquisition, genetic and clinical data collection and analysis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Abell CW, Kwan SW (2001) Molecular characterization of monoamine oxidases A and B. Prog Nucleic Acid Res Mol Biol 65:129–156
2. Ducci F, Newman TK, Funt S, Brown GL, Virkkunen M, Goldman D (2006) A functional polymorphism in the MAOA gene promoter (MAOA-LPR) predicts central dopamine function and body mass index. Mol Psychiatry 11(9):858–866. https://doi.org/10.1038/sj.mp.4001856
3. Sabol SZ, Hu S, Hamer D (1998) A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 103(3):273–279
4. Denney RM, Koch H, Craig IW (1999) Association between monoamine oxidase A activity in human male skin fibroblasts and genotype of the MAOA promoter-associated variable number tandem repeat. Hum Genet 105(6):542–551
5. Wu YH, Fischer DF, Swaab DF (2007) A promoter polymorphism in the monoamine oxidase A gene is associated with the pineal MAOA activity in Alzheimer's disease patients. Brain Res 1167: 13–19. https://doi.org/10.1016/j.brainres.2007.06.053
6. Song DD, Haber SN (2000) Striatal responses to partial dopaminergic lesion: evidence for compensatory sprouting. J Neurosci 20(13):5102–5114
7. Gokturk C, Schultze S, Nilsson KW, von Knorring L, Oreland L, Hallman J (2008) Serotonin transporter (5-HTTLPR) and monoamine oxidase (MAOA) promoter polymorphisms in women with severe alcoholism. Arch Womens Ment Health 11(5–6):347–355. https://doi.org/10.1007/s00737-008-0033-6
8. Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL (2004) MAOA and persistent, pervasive childhood aggression. Mol Psychiatry 9(6):546–547. https://doi.org/10.1038/sj.mp.4001492
9. Derringer J, Krueger RF, Irons DE, Iacono WG (2010) Harsh discipline, childhood sexual assault, and MAOA genotype: an investigation of main and interactive effects on diverse clinical externalizing outcomes. Behav Genet 40(5):639–648. https://doi.org/10.1007/s10519-010-9358-9
10. Ficks CA, Waldman ID (2014) Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR. Behav Genet 44(5):427–444. https://doi.org/10.1007/s10519-014-9661-y
11. Emilsson L, Saetre P, Balciuniene J, Castensson A, Cairns N, Jazin EE (2002) Increased monoamine oxidase messenger RNA expression levels in frontal cortex of Alzheimer's disease patients. Neurosci Lett 326(1):56–60
12. Sparks DL, Woeltz VM, Markesbery WR (1991) Alterations in brain monoamine oxidase activity in aging, Alzheimer's disease, and Pick's disease. Arch Neurol 48(7):718–721
13. Sherif F, Gottfries CG, Alafuzoff I, Oreland L (1992) Brain gamma-aminobutyrate aminotransferase (GABA-T) and monoamine oxidase (MAO) in patients with Alzheimer's disease. J Neural Transm Park Dis Dement Sect 4(3):227–240
14. Gottfries CG, Adolfsson R, Aquilonius SM, Carlsson A, Eckernas SA, Nordberg A, Oreland L, Svennerholm L et al (1983) Biochemical changes in dementia disorders of Alzheimer type (AD/SDAT). Neurobiol Aging 4(4):261–271
15. Storga D, Vrecko K, Birkmayer JG, Reibnegger G (1996) Monoaminergic neurotransmitters, their precursors and metabolites in brains of Alzheimer patients. Neurosci Lett 203(1):29–32
16. Shumay E, Logan J, Volkow ND, Fowler JS (2012) Evidence that the methylation state of the monoamine oxidase A (MAOA) gene predicts brain activity of MAO A enzyme in healthy men. Epigenetics 7(10):1151–1160. https://doi.org/10.4161/epi.21976
17. Postuma RB, Dagher A (2006) Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cereb Cortex 16(10):1508–1521. https://doi.org/10.1093/cercor/bhj088
18. 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. Neurobiol Aging 33(8):1564–1578. https://doi.org/10.1016/j.neurobiolaging.2011.06.007
19. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity

networks for salience processing and executive control. J Neurosci 27(9):2349–2356. https://doi.org/10.1523/jneurosci.5587-06.2007
20. Filippi M, Agosta F, Scola E, Canu E, Magnani G, Marcone A, Valsasina P, Caso F et al (2013) Functional network connectivity in the behavioral variant of frontotemporal dementia. Cortex 49(9): 2389–2401. https://doi.org/10.1016/j.cortex.2012.09.017
21. Menon V (2011) Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15(10):483–506. https://doi.org/10.1016/j.tics.2011.08.003
22. Deschenes CL, McCurry SM (2009) Current treatments for sleep disturbances in individuals with dementia. Curr Psychiatry Rep 11(1):20–26
23. Nyth AL, Gottfries CG (1990) The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry 157:894–901
24. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G et al (2010) Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9(11):1118–1127. https://doi.org/10.1016/s1474-4422(10)70223-4
25. Huang CW, Tsai MH, Chen NC, Chen WH, Lu YT, Lui CC, Chang YT, Chang WN et al (2015) Clinical significance of circulating vascular cell adhesion molecule-1 to white matter disintegrity in Alzheimer's dementia. Thromb Haemost 114(6):1230–1240. https://doi.org/10.1160/th14-11-0938
26. Pinsonneault JK, Papp AC, Sadee W (2006) Allelic mRNA expression of X-linked monoamine oxidase a (MAOA) in human brain: dissection of epigenetic and genetic factors. Hum Mol Genet 15(17):2636–2649. https://doi.org/10.1093/hmg/ddl192
27. Petronis A (2001) Human morbid genetics revisited: relevance of epigenetics. Trends Genet 17(3):142–146
28. Ma ZQ, Bondiolotti GP, Olasmaa M, Violani E, Patrone C, Picotti GB, Maggi A (1993) Estrogen modulation of catecholamine synthesis and monoamine oxidase A activity in the human neuroblastoma cell line SK-ER3. J Steroid Biochem Mol Biol 47(1–6):207–211
29. Wagels L, Votinov M, Radke S, Clemens B, Montag C, Jung S, Habel U (2017) Blunted insula activation reflects increased risk and reward seeking as an interaction of testosterone administration and the MAOA polymorphism. Hum Brain Mapp 38:4574–4593. https://doi.org/10.1002/hbm.23685
30. Lin PH, Tsai SJ, Huang CW, Mu-En L, Hsu SW, Lee CC, Chen NC, Chang YT, et al. (2016) Dose-dependent genotype effects of BDNF Val66Met polymorphism on default mode network in early stage Alzheimer's disease. Oncotarget :https://doi.org/10.18632/oncotarget.11027
31. Fowler JS, Alia-Klein N, Kriplani A, Logan J, Williams B, Zhu W, Craig IW, Telang F et al (2007) Evidence that brain MAO A activity does not correspond to MAO A genotype in healthy male subjects. Biol Psychiatry 62(4):355–358. https://doi.org/10.1016/j.biopsych.2006.08.038
32. McDermott R, Tingley D, Cowden J, Frazzetto G, Johnson DD (2009) Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation. Proc Natl Acad Sci U S A 106(7):2118–2123. https://doi.org/10.1073/pnas.0808376106
33. Kuepper Y, Grant P, Wielpuetz C, Hennig J (2013) MAOA-uVNTR genotype predicts interindividual differences in experimental aggressiveness as a function of the degree of provocation. Behav Brain Res 247:73–78. https://doi.org/10.1016/j.bbr.2013.03.002
34. Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF (2000) A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res 95(1):9–23
35. McGrath LM, Mustanski B, Metzger A, Pine DS, Kistner-Griffin E, Cook E, Wakschlag LS (2012) A latent modeling approach to genotype-phenotype relationships: maternal problem behavior clusters, prenatal smoking, and MAOA genotype. Arch Womens Ment Health 15(4):269–282. https://doi.org/10.1007/s00737-012-0286-y
36. Schulze TG, Muller DJ, Krauss H, Scherk H, Ohlraun S, Syagailo YV, Windemuth C, Neidt H et al (2000) Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. Am J Med Genet 96(6):801–803
37. Yu YW, Tsai SJ, Hong CJ, Chen TJ, Chen MC, Yang CW (2005) Association study of a monoamine oxidase a gene promoter polymorphism with major depressive disorder and antidepressant response. Neuropsychopharmacology 30(9):1719–1723. https://doi.org/10.1038/sj.npp.1300785
38. Du L, Bakish D, Ravindran A, Hrdina PD (2004) MAO-A gene polymorphisms are associated with major depression and sleep disturbance in males. Neuroreport 15(13):2097–2101
39. Arlt S, Demiralay C, Tharun B, Geisel O, Storm N, Eichenlaub M, Lehmbeck JT, Wiedemann K et al (2013) Genetic risk factors for depression in Alzheimer's disease patients. Curr Alzheimer Res 10(1):72–81
40. Fan J, Fossella J, Sommer T, Wu Y, Posner MI (2003) Mapping the genetic variation of executive attention onto brain activity. Proc Natl Acad Sci U S A 100(12):7406–7411. https://doi.org/10.1073/pnas.0732088100
41. Cerasa A, Gioia MC, Labate A, Lanza P, Magariello A, Muglia M, Quattrone A (2008) MAO A VNTR polymorphism and variation in human morphology: a VBM study. Neuroreport 19(11):1107–1110. https://doi.org/10.1097/WNR.0b013e3283060ab6
42. Yu YW, Tsai SJ, Hong CJ, Chen TJ, Yang CW (2004) Association analysis for MAOA gene polymorphism with long-latency auditory evoked potentials in healthy females. Neuropsychobiology 50(4): 288–291. https://doi.org/10.1159/000080954
43. Yu YW, Yang CW, Wu HC, Tsai SJ, Hong CJ, Chen MC, Chen TJ (2005) Association study of a functional MAOA-uVNTR gene polymorphism and personality traits in Chinese young females. Neuropsychobiology 52(3):118–121. https://doi.org/10.1159/000087556
44. Kolla NJ, Dunlop K, Downar J, Links P, Bagby RM, Wilson AA, Houle S, Rasquinha F et al (2016) Association of ventral striatum monoamine oxidase-A binding and functional connectivity in antisocial personality disorder with high impulsivity: a positron emission tomography and functional magnetic resonance imaging study. Eur Neuropsychopharmacol 26(4):777–786. https://doi.org/10.1016/j.euroneuro.2015.12.030
45. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. Science (New York, NY) 297(5582):851–854. https://doi.org/10.1126/science.1072290
46. Holz N, Boecker R, Buchmann AF, Blomeyer D, Baumeister S, Hohmann S, Jennen-Steinmetz C, Wolf I et al (2016) Evidence for a sex-dependent MAOAx childhood stress interaction in the neural circuitry of aggression. Cereb Cortex 26(3):904–914. https://doi.org/10.1093/cercor/bhu249
47. Yu YW, Tsai SJ, Hong CJ, Chen MC, Yang CW, Chen TJ (2005) Association study of a functional MAOA-uVNTR gene polymorphism and cognitive function in healthy females. Neuropsychobiology 52(2):77–82. https://doi.org/10.1159/000086609
48. Camarena B, Rinetti G, Cruz C, Gomez A, de La Fuente JR, Nicolini H (2001) Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive-compulsive disorder. Am J Med Genet 105(3):279–282
49. Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond Ser B Biol Sci 360(1457):1001–1013. https://doi.org/10.1098/rstb.2005.1634