CSF FAM3C- a possible biomarker of Alzheimer's disease

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Abstract

Backgrounnd: The impact of Alzheimer's disease (AD) on the living quality and life expectancy has becoming increasingly severe, but the pathogenesis of AD is still being studied .This study aimed to investigate whether Family with sequence similarity 3 member C (FAM3C), which has been reported to be possibly associated with cognitive function, was associated with the incidence of AD.

Methods: A total of 282 participants from Alzheimer's Disease Neuroimaging Initiative (ADNI) were included. The demographic data, cerebrospinal fluid (CSF) FAM3C content, neuropsychological scores, CSF amyloid protein level, CSF tau protein level, and imaged data were collected. One-way analysis of variance and chi-square test were used to compare demographic data, neuropsychological test scores, CSF protein levels, and imaging data of three groups. Partial correlation analysis and multiple linear regression analysis were used to investigate the relationship between FAM3C and AD diagnostic indicators in different dimensions. An ordered multi-classification logistic regression model was established to determine whether FAM3C is related to the onset of AD.

Results: Lower levels of FAM3C were observed in AD and mild cognitive impairment (MCI) groups. CSF FAM3C level was related to whole-brain atrophy and temporal lobe atrophy, worse cognitive performance, decreased amyloid β 1-42 ($A\beta_{1\text{-}42}$), and lower regional cerebral glucose metabolism.

Conclusion: CSF FAM3C might be a potential diagnostic biomarker of AD. Further study on concrete mechanisms may contribute to early diagnosis and treatment of AD.

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia among the elderly, is an irreversible, progressive neurological disease[1]. At present, there is no cure for AD, only five prescription drugs were approved to intend for symptom management, with varying degrees of efficacy[2]. With the deepening of studies, some theories, such as amyloid β (Aβ) deposition, tau protein abnormality, axonal transport defect, inflammatory response, and cholinergic damage, etc, have been gradually recognized[3–5]. The clinical and genetic trials of more-effective Alzheimer's drugs targeting anti-amyloid, anti-neuroinflammation, anti-tau, or neuroprotection are ongoing. Between 2000 and 2012, more than 400 AD clinical trials were undertaken. Unfortunately, it was suggested that 99.6% of them failed[2]. One potential reason for this result may be that studies were initiated too late in the disease as the pathological changes of AD may appear 10 to 20 years before the appearence of symptoms. Herein lies the promise for more effective AD biomarkers in addition to the well-known Aβ and the tau protein.

Family with sequence similarity 3 member C (FAM3C), also called interleukin-like epithelial-mesenchymal transition inducer (ILEI), is a member of the FAM3 cytokine family which consists of four sequentially similar members (FAM3A, FAM3B, FAM3C and FAM3D)[6]. FAM3C plays an important role in epithelial-mesenchymal transformation (EMT) and tumor metastasis[7, 8]. It has been found overexpressed in colorectal cancer, esophageal cancer, breast cancer, hepatocellular cancer, etc, predicting a poor prognosis[9–12]. Recently, it was indicated that FAM3C may be a risk factor for the development of AD in an animal experiment[13]. However, whether FAM3C is related to AD patients remains to be confirmed.

In this study, we investigated the relationship between AD and cerebrospinal fluid (CSF) FAM3C using data obtained from the Alzheimer's Disease Neuroimaging Initiative database (ADNI).

2. Methods

2.1 ADNI

The ADNI database was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The whole project includes ADNI1, ADNIGO, ADNI2 and ADNI3 research stages. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease. For up-to-date information, see www.adni-info.org.

2.2 Participants

In this study, we included participants who underwent lumbar puncture for quantitative detection of CSF proteins from baseline ADNI1 cohort. A total of 282 participants were included and the general inclusion criteria were as follows: (1) normal controls (NC): 55–90 years old, Mini-Mental State Exam (MMSE) scores between 24–30, a Clinical Dementia Rating (CDR) of 0, non-depressed, non-MCI and non-demented. (2) patients with MCI: 55–90 years old, MMSE scores between 24–30, a memory complaint, have objective memory loss measured by education-adjusted scores on Wechsler Memory Scale-Revised (WMS-R) Logical Memory II, a CDR of 0.5, absence of significant enough levels of impairments in other cognitive domains so that the criteria for dementia are not met, largely preserved activities of daily living, and an absence of dementia. (3) patients with AD: 55–90 years old, MMSE between 20 and 26, memory dysfunction is the same to MCI, a CDR of 0.5 or 1.0. More detailed inclusion and exclusion criteria are available in ADNI1 Clinical Protocols obtained from http://adni.loni.usc.edu/.

2.3 *APOE* genotypes

There are three common *APOE* alleles: ε2, ε3 and ε4. *APOE4* gene has been accepted as a risk factor for late-onset and sporadic AD. At baseline, venous blood of all participants was collected and the *APOE* genotype was determined. In this study, subject possessing one or two *APOE4* alleles was considered as an *APOE4* carrier.

2.4 Neuropsychological assessment

According to AD diagnostic criteria, neuropsychological assessment of AD consists of cognitive impairment, social and daily functioning decline, and psychosocial behavioral symptoms. The decline of cognitive function was mainly determined by various psychological scales in clinical practice. Qualified ADNI staff conducted more than a dozen scale tests on each participant at the screening stage and then derived composite scores for executive functioning (EF) and memory (MEM) using data from the ADNI neuropsychological battery according to item response theory (IRT). This study included the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) and Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-Cog) scores, as well as composite scores EF and MEM. Higher MMSE, MEM and EF scores reflect better cognitive function while higher CDR and ADAS-cog scores reflect worse cognitive function.

2.5 CSF FAM3C, tau and Aβ

All of the 282 participants included in our study underwent lumbar puncture to obtain CSF baseline data. CSF samples were analyzed by the electrochemiluminescence immunoassays (ECLIA) for CSF total tau (T-tau), phosphorylated tau 181 (P-tau181), and amyloid β 1–42 ($A\beta_{1-42}$). It should be noted that the elecsys $A\beta_{1-42}$ immunoassay in use is an assay that is currently under development and for investigational use only, therefore it is excluded for clinical decision making or derivation of medical decision points. The quantification of CSF FAM3C was conducted by the use of liquid chromatography-tandem mass spectrometry with multiple reaction monitoring (LC/MS-MRM) approach. The whole MRM panel consisted of 567 peptides representing 221 proteins, and peptide sequence used for FAM3C was GINVALANGK in our research. The output results are reported in arbitrary signal intensity units on a natural log scale in

a form of “log peptide intensity”. Detailed data was shown in the Biomarkers Consortium CSF Proteomics MRM data set in the official website.

2.6 Neuroimaging data

All of the ADNI participants received structural MRI examinations at baseline and quite a few of them had follow-up visits. Tensor-based morphometry (TBM) was used to analyze cross-sectional and longitudinal MRI data of bilateral temporal lobes. Iterative principal component analysis (IPCA) was practiced to show the numerical value of the whole-brain atrophy rate from baseline to 12 months. This study included typical MRI results such as total brain volume, lobe volume, ventricular volume, cortical thickness at baseline as well as follow-up visits. Baseline spatial pattern of abnormalities of recognition of early AD (SPARE-AD) scores which provided a predictive value of cognitive decline and conversion of NC to AD were also obtained. Approximately 50% of participants had a fluorodeoxyglucose (FDG) PET scan. Based on coordinates frequently cited in other FDG studies comparing AD, MCI, and NC, FDG PET results of angular gyrus, posterior cingular and inferior temporal gyrus were obtained in this study.

2.7 Statistical methods

One-way analysis of variance and chi-square test were used to compare demographic data, neuropsychological test scores, CSF protein levels and imaging data of three groups. Partial correlation analysis and multiple linear regression analysis were used to investigate the relationship between FAM3C and AD diagnostic indicators in different dimensions. An ordered multi-classification logistic regression model was established to determine whether FAM3C is related to the occurrence and progression of AD. P-value < 0.05 was statistically significant. All statistical analyses were conducted by SPSS 22.0.

3. Results

3.1 Demographic and clinical data

The information of age, gender, education, *AOPE4*, neuropsychological test scores, CSF T-tau, P-tau181, $A\beta_{1-42}$ and FAM3C content are shown in Table 1. There was no statistical difference in age, sex and education years among three groups. In Table 1, “yes” means the subject was an *APOE4* carrier. It can be seen that the ratio of *APOE4* carriers to non-carriers increased successively in NC group, MCI group and AD group. The MMSE score, MEM score and EF score decreased while the CDR score and ADAS score increased. These neuropsychological results displayed the declined cognitive function in patients with AD and MCI, compared with the normal group. The increase of CSF T-tau, P-tau181 and decrease of CSF $A\beta_{1-42}$ in AD and MCI groups was consistent with numerous previous studies. One-way ANOVA results demonstrated that FAM3C content among the three groups was statistically significant. CSF FAM3C concentration was lower in AD and MCI groups compared to that of NC group. The pairwise comparison results of FAM3C among the three groups were also statistically significant (NC group versus AD group:P = 0.019, MCI group versus AD group:P = 0.042).

Table 1
Demographic and clinical data of all participants

Characteristics	NC(n = 84)	MCI(n = 134)	AD(n = 64)	Total(n = 282)	P-value
Sex(male/female)	43/41	90/44	36/28	169/113	0.051
Age(years)	75.74 ± 5.59	74.62 ± 7.32	75.19 ± 7.56	75.08 ± 6.90	0.507
Education (years)	15.68 ± 2.99	16.03 ± 2.96	15.05 ± 2.98	15.70 ± 2.99	0.095
APOE4 (yes/no)	20/64	71/63	45/19	136/146	< 0.001
MMSE	29.02 ± 1.02	26.90 ± 1.74	23.48 ± 1.87	26.76 ± 2.55	< 0.001
CDR	0.00 ± 0.00	0.50 ± 0.00	0.73 ± 0.25	0.40 ± 0.30	< 0.001
ADAS	9.24 ± 4.25	19.02 ± 6.04	28.88 ± 7.46	18.30 ± 9.23	< 0.001
MEM	0.99 ± 0.50	-0.15 ± 0.57	-0.89 ± 0.55	0.02 ± 0.89	< 0.001
EF	0.60 ± 0.73	-0.10 ± 0.79	-1.02 ± 0.90	-0.10 ± 0.99	< 0.001
T- Tau (pg/mL)	241.39 ± 76.62	317.59 ± 118.48	361.44 ± 129.41	304.85 ± 118.93	< 0.001
P- tau181 (pg/mL)	22.20 ± 8.01	31.51 ± 13.59	36.38 ± 15.19	29.84 ± 13.66	< 0.001
$A\beta_{1-42}$ (pg/mL)	1323.75 ± 652.53	819.85 ± 450.40	637.84 ± 345.45	928.64 ± 565.78	< 0.001
FAM3C (natural log intensity)	18.63 ± 0.37	18.60 ± 0.40	18.46 ± 0.47	18.57 ± 0.41	0.026

Data are presented as mean ± standard deviation or participants. P-values are for one-way analysis of variance or chi-square test (categorical variables).

Abbreviations: APOE4, apolipoprotein E4; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; ADAS, Alzheimer's Disease Assessment Scale; MEM, memory; EF, executive functioning; T-tau, total tau; P-tau181, phosphorylated tau 181; Aβ1–42, amyloid beta-protein 1–42; FAM3C, Family with sequence similarity 3 member C.

3.2 Logistic regression analysis

The ordered multivariate logistic regression model was established to analyze the influence of FAM3C on the incidence of AD since NC, MCI and AD can be regarded as three development stages indicating the disease status. Based on the above one-way ANOVA results, FAM3C, $A\beta_{1-42}$, P-tau181, APOE4 were included in the model. T-tau was excluded because of a strong linear relationship with P-tau181. Test of parallel lines (X^2 = 7.143, P = 0.129) and model fitting information result (X^2 = 108.469, P < 0.001) indicated the model was statistically significant. Decreased FAM3C, decreased $A\beta_{1-42}$, and increased P-tau181 were AD risk factors according to this model. The parameter estimation result demonstrated that CSF FAM3C content was associated with the possibility of MCI and AD. When AD group is set as the control group, the regression coefficient B was − 1.514 (Exp(B) = 0.220, P < 0.001, 95%CI: 0.097 ~ 0.501). When

the natural log intensity of CSF FAM3C decreased one, the likelihood of developing from MCI to AD increased by 78.0%, and the likelihood of progression from NC to MCI increased by the same degree.

3.3 FAM3C and Neuropsychological scale scores

FAM3C was found to be statistically significant related to neuropsychological scale scores. In partial correlation analysis, T-tau, P-tau181 and $A\beta_{1-42}$ were set as the control variables. The results showed that higher FAM3C level was associated with higher MEM result ($r = 0.273$, $P < 0.001$), EF score ($r = 0.148$, $P = 0.014$) and lower ADAS score($r=-0.288$, $P < 0.001$). Spearman correlation analysis showed that higher FAM3C level was associated with higher MMSE score ($r = 0.169$, $P = 0.005$) and lower CDR scpre ($r=-0.144$, $P = 0.016$). In multiple linear regression analyses, FAM3C, P-tau181 and $A\beta_{1-42}$ had a statistically significant effect on MEM and ADAS scores. A positive linear correlation could be established between FAM3C and MEM (adjusted $R^2 = 0.295$, $B = 0.553$, $P < 0.001$, 95% CI: 0.273 ~ 0.834), indicating that higher FAM3C level was associated with better memory ability (Fig. 1). At the same time, a negative linear correlation existed between FAM3C and ADAS (adjusted $R^2 = 0.290$, $B=-6.093$, $P < 0.001$, 95% CI: -9.045~-3.140), indicating that lower FAM3C level was associated with worse cognitive function (Fig. 2).

3.4 FAM3C and Aβ1–42

The content of CSF FAM3C and $A\beta_{1-42}$ changed in the same direction (Pearson correlation coefficient was 0.359, $P < 0.001$). A positive linear regression model (adjusted $R^2 = 0.126$, $B = 492.670$, $P < 0.001$, 95% CI:341.952 ~ 643.387) could be established as shown in Fig. 3.

3.5 FAM3C and MRI results

Craniocerebral MRI examination indexes including volume of total brain parenchyma, ventricles and hippocampus, the thickness of temporal lobe, fusiform gyrus and entorhinal cortex were collected. Longitudinal data showed the rates of total brain atrophy, temporal lobe atrophy and composite prediction index SPARE-AD were also obtained. The above indicators were significantly different in NC, MCI and AD groups, revealing that the brain structure atrophy was worse in AD and MCI patients than in normal aging. Partial correlation analysis and multiple linear regression analysis results between FAM3C and structure MRI data are shown in Table 2. Right hippocampus volume, bilateral temporal lobe thickness except for left middle temporal, right fusiform gyrus thickness, bilateral entorhinal cortex thickness were found to have a positive linear correlation with CSF FAM3C content at baseline. Total ventricle volume and lateral ventricle volume had a negative linear correlation with CSF FAM3C content at baseline. In this study, no significant correlation was found between FAM3C and total brain parenchyma volume as well as left hippocampus volume. In the longitudinal view, FAM3C was negatively correlated with the 12-month whole brain atrophy rate represented by IPCA in Table 2. Moreover, the follow-up temporal lobe volume ratios to baseline were calculated after one year (adjusted $R^2 = 0.330$) and two years (adjusted $R^2 = 0.411$), and it was found that both of them had a positive linear relationship with FAM3C, that is, the reduction of FAM3C was moderately correlated with temporal lobe atrophy. In predicting the likelihood of AD, the SPARE-AD score was negatively related to baseline FAM3C content. In general, the content of baseline FAM3C in this study was negatively correlated with brain atrophy, especially bilateral temporal lobe atrophy.

Table 2
Partial correlation analysis and multiple linear regression analysis results of FAM3C and structure MRI data

Item	N	R	P*	Adjusted R^2	F	B	P**	95% CI
total cranial volume	279	0.080	0.185	-	-	-	-	-
ventricles volume	258	-0.174	0.005	0.123	12.964	-9566.219	0.11	-16897.302~-2235.135
left hippocampus volume	258	0.105	0.094	-	-	-	-	-
right hippocampus volume	258	0.218	< 0.001	0.087	9.171	322.818	0.004	102.888 ~ 542.748
left inferior lateral ventricle volume	258	-0.184	0.003	0.104	10.894	-419.594	0.009	-731.170~-108.019
right inferior lateral ventricle volume	258	-0.257	< 0.001	0.130	13.801	-617.096	< 0.001	-940.665~-293.527
left middle temporal thickness	258	0.156	0.013	0.087	9.124	0.081	0.055	-0.002 ~ 0.164
right middle temporal thickness	258	0.190	0.002	0.124	13.097	0.104	0.012	0.023 ~ 0.185
left inferior temporal thickness	258	0.174	0.005	0.114	12.017	0.090	0.034	0.007 ~ 0.173
right inferior temporal thickness	258	0.227	< 0.001	0.122	12.959	0.129	0.002	0.048 ~ 0.210
left fusiform thickness	258	0.150	0.017	0.095	10.025	0.070	0.078	-0.008 ~ 0.148
right fusiform thickness	258	0.245	< 0.001	0.130	13.848	0.134	< 0.001	0.059 ~ 0.208
left entorhinal thickness	258	0.159	0.011	0.108	11.390	0.199	0.038	0.011 ~ 0.387
right entorhinal thickness	258	0.271	< 0.001	0.156	16.826	0.386	< 0.001	0.196 ~ 0.576
IPCA	239	-0.195	0.003	0.140	13.948	-0.110	0.002	-0.181~-0.040

-: Multiple linear regression analysis wasn't conducted for items which showed no statistical significance in Partial correlation analysis.

Abbreviations: N, number of participants; R, partial correlation coefficient; P*, P value of partial correlation analysis; Adjusted R2, value of adjusted R2 in multiple linear regression analysis; F, F value of multiple linear regression analysis; B, coefficient B value of multiple linear regression analysis; P**, P value of B in multiple linear regression analysis; 95% CI, 95% confidence interval of B; IPCA, percent annualized whole brain atrophy detected by Iterative Principal component Analysis; TEMPVOLRATIO1, bilateral temporal lobe volume to baseline volume ratio one year later; TEMPVOLRATIO2, bilateral temporal lobe volume to baseline volume ratio two years later; SPARE-AD, spatial pattern of abnormalities of recognition of early AD.

Item	N	R	P*	Adjusted R^2	F	B	P**	95% CI
TEMPVOLRATIO1	267	0.273	< 0.001	0.330	44.629	9.032	< 0.001	4.677 ~ 13.388
TEMPVOLRATIO2	225	0.368	< 0.001	0.411	53.049	21.371	< 0.001	14.007 ~ 28.736
SPARE-AD	282	-0.279	< 0.001	0.231	29.129	-1.300	< 0.001	-1.904~-0.696

-: Multiple linear regression analysis wasn't conducted for items which showed no statistical significance in Partial correlation analysis.

Abbreviations: N, number of participants; R, partial correlation coefficient; P*, P value of partial correlation analysis; Adjusted R2, value of adjusted R2 in multiple linear regression analysis; F, F value of multiple linear regression analysis; B, coefficient B value of multiple linear regression analysis; P**, P value of B in multiple linear regression analysis; 95% CI, 95% confidence interval of B; IPCA, percent annualized whole brain atrophy detected by Iterative Principal component Analysis; TEMPVOLRATIO1, bilateral temporal lobe volume to baseline volume ratio one year later; TEMPVOLRATIO2, bilateral temporal lobe volume to baseline volume ratio two years later; SPARE-AD, spatial pattern of abnormalities of recognition of early AD.

3.6 FAM3C and cerebral glucose metabolism

In this study, 37 normal controls, 72 MCI patients, and 36 AD patients accepted FDG PET scan at baseline. The results showed that mean value of glucose metabolism decreased in MCI group and further decreased in AD group (Fig. 4). In multiple linear regression, FAM3C was found to have a positive linear relationship with mean glucose metabolism of left angular gyrus (adjusted R^2 = 0.075, B = 0.093, P = 0.031, 95% CI:0.009 ~ 0.177), right angular gyrus (adjusted R^2 = 0.110, B = 0.099, P = 0.013, 95% CI:0.021 ~ 0.176), bilateral posterior cingular (adjusted R^2 = 0.075, B = 0.113, P = 0.011, 95% CI:0.026 ~ 0.200), left temporal gyrus (adjusted R^2 = 0.150, B = 0.130, P = 0.001, 95% CI:0.058 ~ 0.202), right temporal gyrus (adjusted R^2 = 0.116, B = 0.093, P = 0.005, 95% CI:0.028 ~ 0.157).

4. Discussion

In the present study, we analyzed the data from ADNI database and determined the relationship between cerebrospinal fluid FAM3C level and Alzheimer's Disease. The current study provides novel evidence that decreased CSF FAM3C level in AD and MCI patients, in relation to the extent of whole-brain atrophy and temporal lobe atrophy, and positively relating to CSF $A\beta_{1-42}$ and regional brain glucose metabolism, may contribute to worsening cognitive function of the AD patients.

As a novel marker, the role of FAM3C has not been fully elucidated. It was demonstrated that FAM3C played an important role in bone metabolism, via modulating osteogenic differentiation by down-regulating Runx2[10]. Moreover, the single-nucleotide polymorphism in gene Fam3c was found to be associated with bone mineral density at the wrist and other sites in the skeleton[14]. Recently, there has been increasing evidence that FAM3C is an important regulator of glucose and lipid metabolism. It was shown that FAM3C suppressed hepatic gluconeogenesis and lipogenesis through activating the HSF1-CaM-Akt pathway and repressing the mTOR-SREBP1-FAS pathway[15]. In obese diabetic mice, FAM3C expression was reduced in the liver[16]. Furthermore, FAM3C genetic variants were found to be associated with dyslipidemia and lipid traits among Chinese children[17]. What's more, FAM3C has been shown to be strongly up-regulated in several cancers including gastric cancer, melanoma, colon and breast cancer, oral and esophageal squamous cell carcinoma, essential for EMT and metastasis formation, and alter subcellular localization strongly correlating with poor survival[8, 9, 12, 18, 19]. It has been indicated that the FAM3C-YY1-HSF1 pathway exerted an

important role in TGF β-triggered proliferation and migration of human breast cancer cells[11, 20]. In addition, FAM3C is involved in retinal laminar formation in vertebrates and may relate to cell differentiation and proliferation during inner ear embryogenesis[21, 22].

Some studies of FAM3C concentrating on brain were performed and FAM3C was found to be widely expressed in mice brain including cortex, hippocampus, amygdala, striatum, thalamus, hypothalamus, cerebellum and brainstem[13]. Autopsy and immunohistochemical results of the human brain and monkey brain showed that FAM3C was widely distributed in neurons and ependymal cells, but not in glial cells and vascular endothelial cells. FAM3C levels in CSF peaked after birth and then decreased with age, but significantly decreased under the pathological condition of AD. It was identified that FAM3C could inhibit the deposition of Aβ. And transgenic overexpression of FAM3C significantly reduced the brain Aβ burden and ameliorated the memory deficit in AD model mice[13]. The study is consistent with ours, which indicates that FAM3C may be a probable target for AD therapy.

As for the diagnostic criteria for AD, the latest ones are the 2011 NIA-AA criteria, published by the National Institute of Aging (NIA) and the Alzheimer's Association (AA). The new standard includes biomarkers in the diagnostic criteria for AD, such as changes in CSF Aβ, T-tau, P-tau and the amyloid changes shown in PET, decreased uptake of 18FDG in the temporal-parietal cortex, and atrophy in the medial temporal lobe shown by structural MRI[23]. These markers are mainly related to two major pathological features of AD - neurofibrillary tangles (NFT) and senile plaques (SP). The NFT is accumulated by the intraneuronal accumulation of tau proteins in phosphorylated form and the accumulation and deposition of Aβ are involved in the formation of senile plaque[24]. Although still controversial, these markers provide some supporting roles in the diagnosis of AD. But the diagnosis of MCI and AD is still based more on neuropsychological tests and neurological examination. Memory impairment is often the first chief complaint of AD. After the onset of AD, the hippocampus and entorhinal cortex were initially involved, followed by the medial parietal cortex, the lateral temporal cortex, and the frontal lobe. Finally, the lesion developed to the entire cerebral cortex. Cortical atrophy was mainly manifested in narrowed gyrus, widened sulcus, thinning cortex, varying degrees of atrophy of white matter and enlargement of lateral ventricle[25]. In this study, FAM3C showed a certain degree of association with the above characteristics of AD, which may be involved in the pathogenesis of AD.

Due to the invasive operation of lumbar puncture and the time cost of imaging examination, the sample size of this study was relatively limited. Moreover, it was only an observational study and long-term clinical studies and experimental studies are needed in the future.

5. Conclusion

In summary, this study has provided the new evidence that FAM3C might be a potential point of penetration of AD pathogenesis. Further study on the concrete mechanisms of FAM3C and cognitive impairment may have innovative significance in exploring the pathogenesis, early diagnosis and treatment of AD.

Abbreviations

AD Alzheimer's disease

FAM3C Family with sequence similarity 3 member C

ADNI Alzheimer’s Disease Neuroimaging Initiative

CSF cerebrospinal fluid

Aβ1–42 amyloid β 1–42

MCI mild cognitive impairment

ILEI nterleukin-like epithelial-mesenchymal transition inducer

EMT epithelial-mesenchymal transformation

MRI magnetic resonance imaging

PET positron emission tomography

NC ormal controls

MMSE Mini-Mental State Exam

CDR Clinical Dementia Rating

WMS-R Wechsler Memory Scale-Revised

APOE apolipoprotein E

EF executive functioning

MEM memory

IRT item response theory

ECLIA electrochemiluminescence immunoassays

T-tau total tau T-tau

P-tau181 phosphorylated tau 181

LC/MS-MRM liquid chromatography-tandem mass spectrometry with multiple reaction monitoring

TBM Tensor-based morphometry

IPCA Iterative principal component analysis

SPARE-AD spatial pattern of abnormalities of recognition of early AD

FDG fluorodeoxyglucose

NIA National Institute of Aging

AA Alzheimer's Association

NFT neurofibrillary tangles

SP senile plaques

Declarations

Ethics approval and consent to participate

All participants in ADNI provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All of the original data included in this study were available in the ADNI database.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provide data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply_/ADNI_Acknowledgement_List.pdf

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Chunmei Bian: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

Liping Wang: Analysis or interpretation of the data.

Zhenzhen Long: Analysis or interpretation of the data.

Ping Xue: Major role in the acquisition of data.

Siming Guan: Major role in the acquisition of data.

Wei Li: Interpreted the data; revised the manuscript for intellectual content.

All authors read and approved the final manuscript.

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Figures

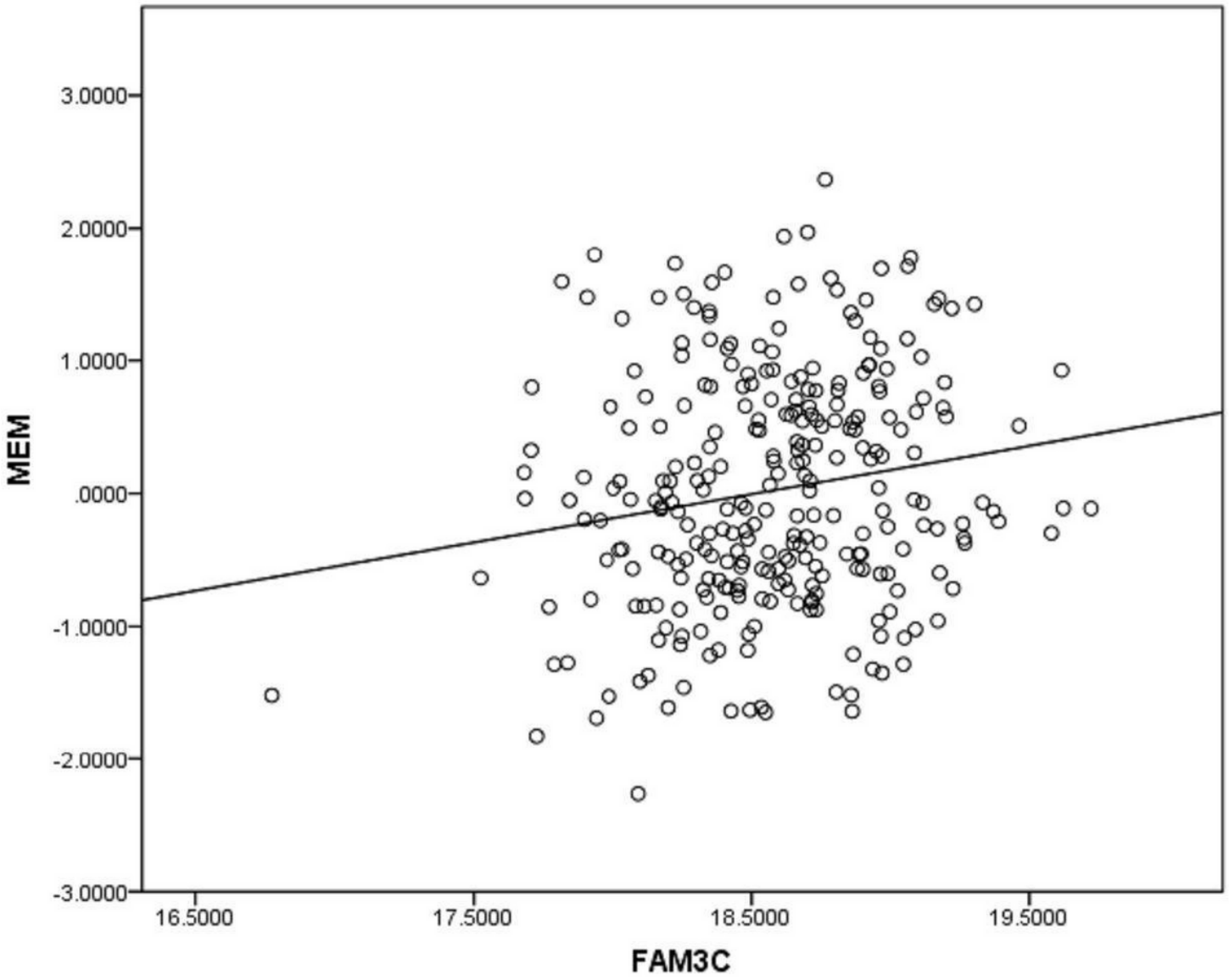

Figure 1

Scatter plot and total fitting line of CSF FAM3C and MEM score

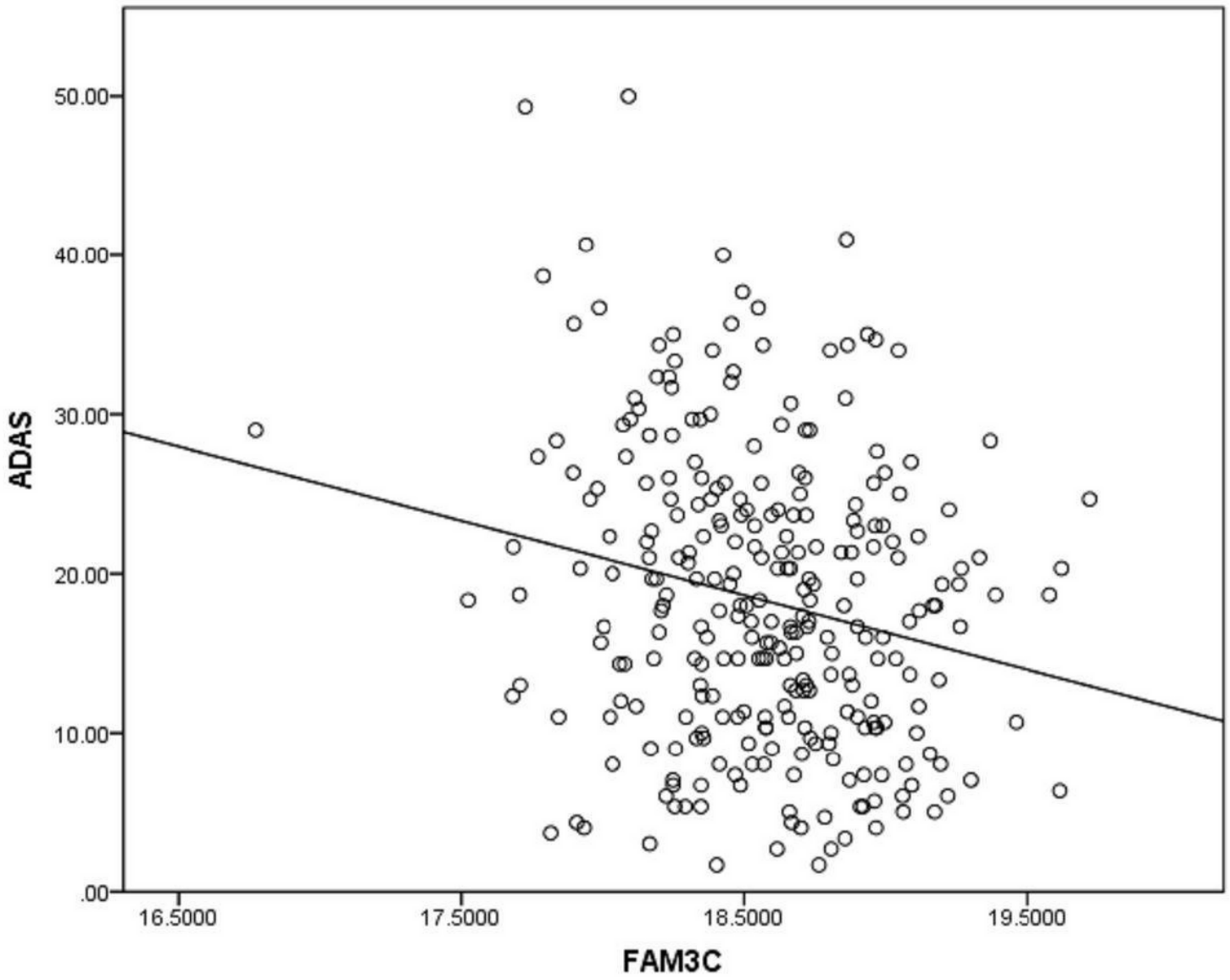

Figure 2

Scatter plot and total fitting line of CSF FAM3C and ADAS score

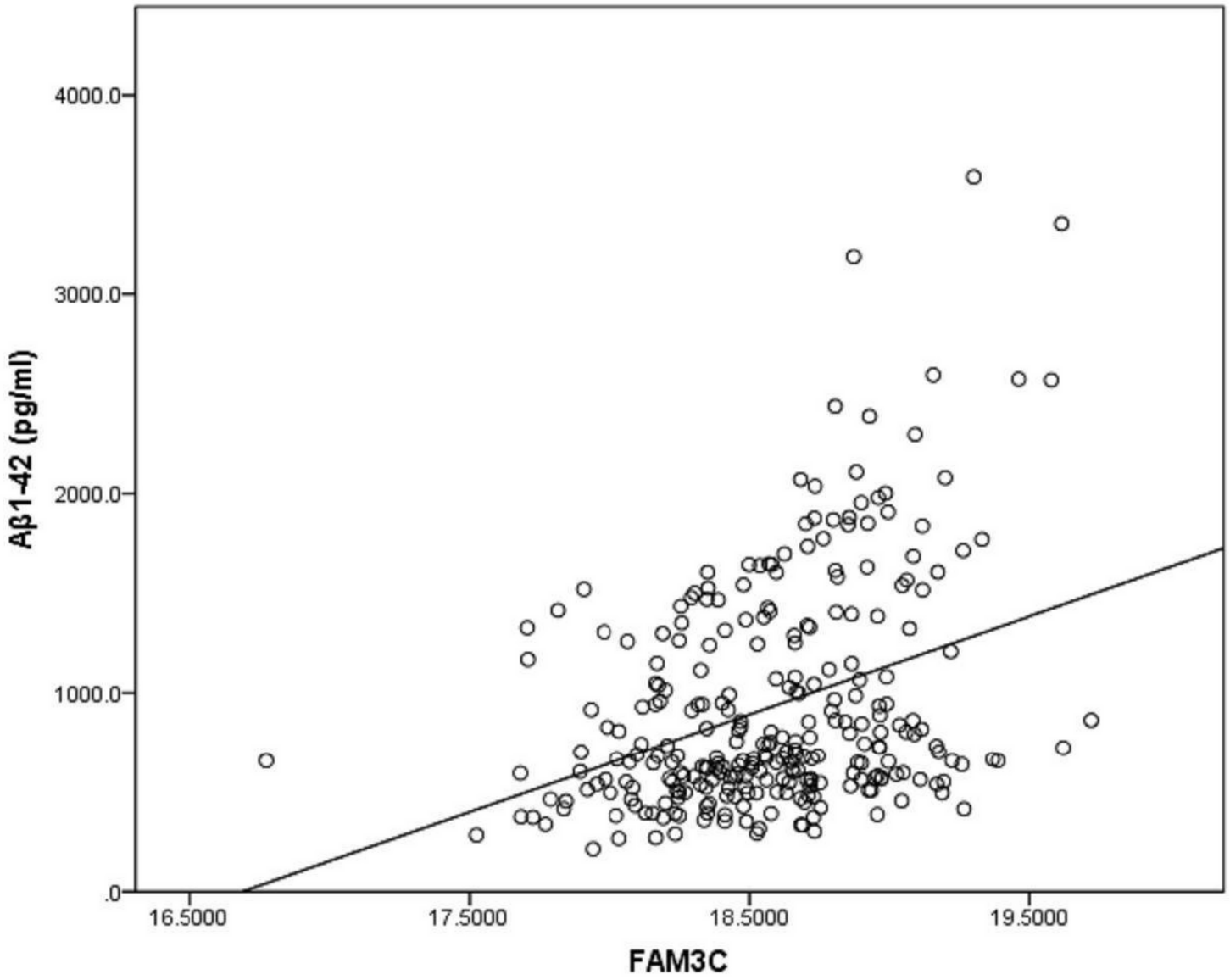

Figure 3

Scatter plot and total fitting line of CSF FAM3C and Aβ1-42(pg/ml)

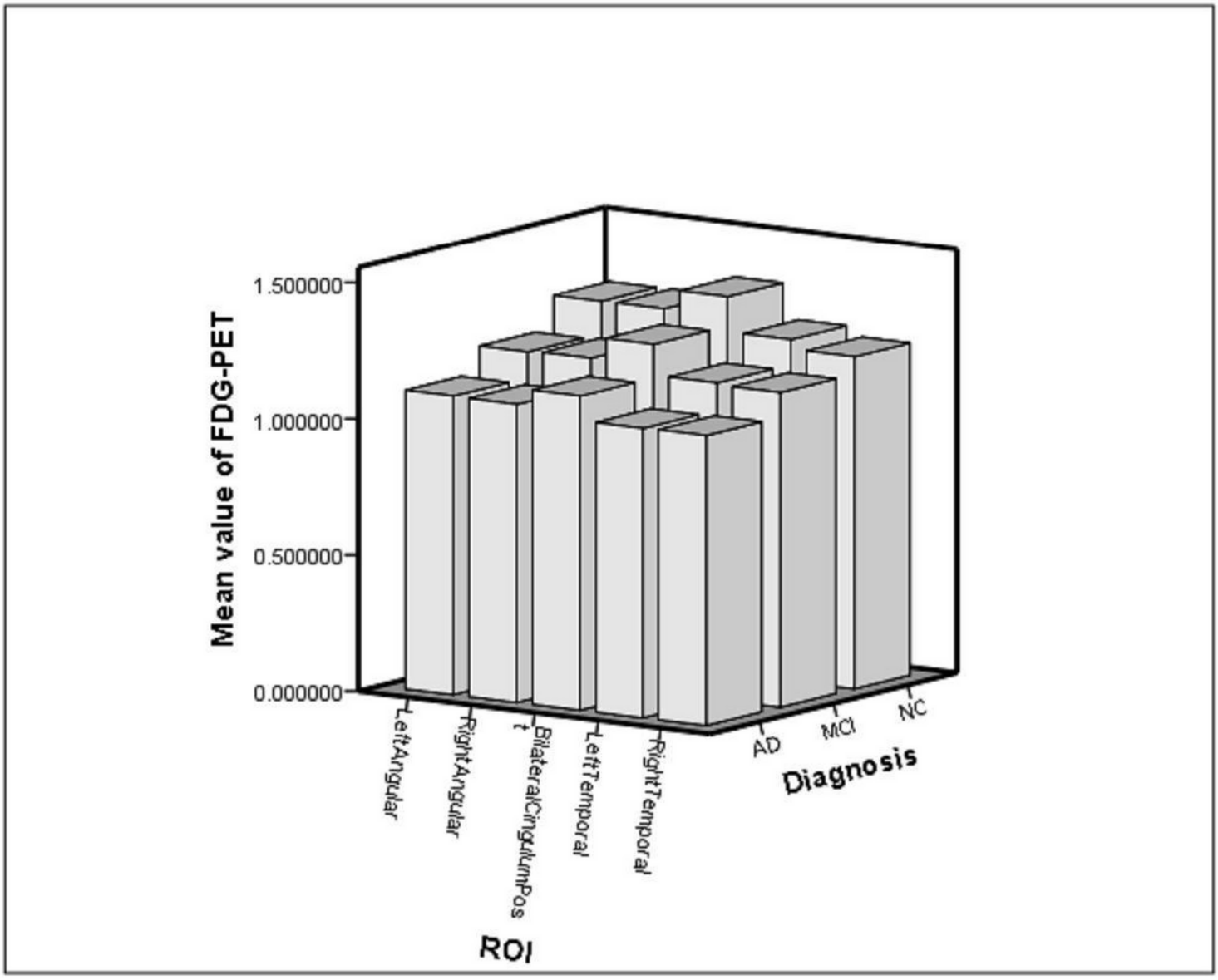

Figure 4

3D bar charts of glucose metabolism measured by FDG-PET in five ROI (region of interest). All of the five regions showed a decreasing tendency in AD group and MCI group compared to NC group.