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Research paper

Associations of Subsyndromal Symptomatic Depression with Cognitive Decline and Brain Atrophy in Elderly Individuals without Dementia: A Longitudinal Study

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ABSTRACT

Background: Subsyndromal symptomatic depression (SSD) is prevalent in older adults. However, it remains unclear whether there are effects of SSD on brain aging outcomes (cognition and brain structures), especially in the presence of Alzheimer's Disease (AD) pathology.

Methods: A total of 1,188 adults without dementia were recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Participants with SSD were measured using the 15-item Geriatric Depression Scale (GDS-15). In multivariable models, the cross-sectional and longitudinal associations of SSD with brain aging outcomes were explored. We further evaluated whether baseline amyloid-β (Aβ) load modifies the relations between SSD and brain aging outcomes.

Results: SSD at baseline was associated with significantly longitudinal decline in cognition and displayed significantly accelerated atrophy in hippocampus ($\beta = -29.53$, $p = 0.001$) and middle temporal gyrus ($\beta = -77.82$, $p = 0.006$) among all participants and Aβ-Positive individuals. SSD interacted with baseline Aβ load in predicting longitudinal decline in Mini Mental State Examination (MMSE) ($\beta = -0.327$, $p = 0.023$), episodic memory ($\beta = -0.065$, $p = 0.004$) and increase in Alzheimer's Disease Assessment Scale Cognition 13-item scale (ADAS-cog13) ($\beta = 0.754$, $p = 0.026$).

Limitations: Our study didn't look at AD diagnosis but Aβ status.

Conclusions: Our findings suggested that older people without dementia with both SSD and a high level of Aβ load may have higher risk of cognitive deterioration and brain atrophy. Therapeutic mitigation of depressive symptoms, especially in those with abnormal Aβ levels, may help delay progressive decline in cognition.

1. Introduction

Late-life depression (LLD) has been found a risk factor for cognitive deterioration and has been associated with an approximate 2-fold increase in incident dementia (Diniz et al., 2013). There's emerging evidence indicating that depressive symptoms, including those in the minimal and mild range, are troubling and prevalent among older individuals (Laborde-Lahoz et al., 2015; Mackin et al., 2012). These symptoms might also be considered as modifiers or clinical indicators of cognitive performance or Alzheimer's Disease (AD). There's limited longitudinal research showing that each reported depressive symptom increased the risk of AD by 19% (Sarnowski et al., 2018). Subsyndromal symptomatic depression (SSD) is previously defined as the presence of depressive symptoms at an intensity or frequency not consistent with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria for major or minor depression (Lyness et al., 2009). The prevalence of SSD for older community-dwelling adults is generally estimated at 15% percent and in mild cognitive impairment (MCI) estimated up to 50% percent (Zhao et al., 2016). However, the effect of SSD on cognition and neurodegeneration is not well understood. The

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association between depressive symptoms and cognitive decline has been established in previous studies among older individuals, but the association was restricted to cross-sectional analysis, limiting inferences of causality (Gonzales et al., 2018). In addition, the association between SSD and brain aging outcomes, especially in the presence of AD pathology, hasn't been established among older people without dementia. More comprehensive understanding of the associations among SSD, brain aging outcomes, and AD pathology plays a crucial role in prognosing among older adults who have depressive symptoms and may be at high risk for cognitive deterioration. In this study, we sought to evaluate the cross-sectional and longitudinal associations of SSD with cognition and brain structures. We also aimed to explore whether baseline amyloid load modified the associations between SSD and cognition and brain imaging biomarkers among older people without dementia. Based on prior studies, in cognitive healthy older adults, the presence of abnormal levels of amyloid-β (Aβ) is associated with decline in cognition and higher rates of progression to mild cognitive impairment or dementia (Lim et al., 2014). Depressive symptoms are related to increased Aβ and cognitive deterioration (Byers and Yaffe, 2011). We hypothesized that SSD would be significantly associated with cognitive decline and brain atrophy, and the effects would be stronger in those with Aβ-Positive status.

2. Material and methods

2.1. ADNI

All data used in this study (including the medical history, baseline demographic characteristics, biomarkers) were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI is a multicenter study which is designed to develop clinical assessments, genetic, imaging and biochemical biomarkers for the study of AD. The participants are adults aged 55–90 years with Alzheimer's Disease (AD), mild cognitive impairment (MCI) and without cognitive impairment. More information can be obtained at http://www.adni-info.org/ or in prior reports (Jack et al., 2010; Jagust et al., 2010).

2.2. Participants

All participants included in our study were recruited from ADNI-1, ADNI-2, and ADNI-GO. Here, we restricted the present analyses to participants without cognitive impairment and with MCI whose baseline Geriatric Depression Scale (GDS) scores were available. Exclusion criteria at baseline included: (1) insufficient data on sociodemographic characteristics; (2) psychiatric illness or neurological disease other than AD; (3) the presence of major depression or significant symptoms of depression (GDS > 5). Finally, we included 1,188 older people without dementia in our study, including 455 without cognitive impairment and 733 with MCI at baseline. The inclusion criteria for individuals without cognitive impairment or with MCI in ADNI was described in detail previously (Bertens et al., 2017; Petersen et al., 2010). Participants were classified into Aβ-Positive (N = 511) and Aβ-Negative (N = 372) groups (according to the baseline levels of Aβ measured in cerebrospinal fluid (CSF) or on 18F-AV-45-PET. Aβ-Positive was defined as the concentration of CSF ≤ 192pg/ml or a florbetapir standard uptake value ratio (SUVR) above 1.11 using the whole cerebellum reference region on 18F-AV-45-PET according to previous report (Clark et al., 2011; Mattsson et al., 2014; Palmqvist et al., 2016). For 305 individuals, we did not have any information of Aβ markers, and therefore they could not be classified into Aβ-Positive or Aβ-Negative group.

2.3. Assessment of depressive and anxiety symptoms

The 15-item version of the Geriatric Depression Scale (GDS-15) was used to assess depressive symptoms in the ADNI study (Yesavage et al., 1982). The total scores of GDS range from 0 to 15; higher scores on the GDS reflect greater depression. Scores of 6 or higher on this scale indicate clinically meaningful depression (Marc et al., 2008; Yesavage, 1988). Based on baseline GDS scores, participants with SSD were defined with a score of 1–5 and healthy controls (HC) with a score of 0 on the basis of prior studies (Bertens et al., 2017). Neuropsychiatric Inventory Questionnaire (NPI-Q) was used to assess anxiety symptoms (Kaufer et al., 2000). Individual with anxiety symptoms was defined as having a score of 1 on the anxiety domain. Medical history at baseline were obtained at the initial visit by self-report.

2.4. CSF measurements

Data of CSF biomarkers used in our analysis were obtained from the ADNI dataset. The method for data acquisition was described previously (Shaw et al., 2009). In sum, CSF was collected by lumbar puncture and then carried to ADNI Biomarker Core laboratory on dry ice. CSF Aβ, total tau, and p-tau were measured using Innogenetics (INNOBIAAlzBio3; Ghent, Belgium) immunoassay kit-based reagents. The within-batch precision values were <10% (5.1–7.8% for Aβ42, 4.4–9.8% for total tau and 5.1–8.8% for p-tau, respectively).

2.5. 18F florbetapir AV45 PET imaging

Florbetapir data in our analysis was downloaded from ADNI (http://adni.loni.usc.edu/). The data preprocessing is available online (adni.loni.ucla.edu/about-data-samples/image-data). Co-registering the florbetapir scan to the corresponding MRI was used to calculate the mean florbetapir AV45 uptake (reflecting the Aβ deposition) within each grey matter region. And florbetapir SUVRs can be created as a mean binding of four cortical grey matter regions (cingulate, frontal, lateral temporal, lateral parietal), divided by reference region (whole cerebellum). More details of the region-of-interest protocol and PET acquisition have been reported previously (Apostolova et al., 2010).

2.6. Cognitive measurement

In the ADNI study, calculation of executive function and episodic memory composite measures has been described in detail previously. The memory (ADNI-MEM) and executive function (ADNI-EF) composite score were leveraged in our present analyses (Crane et al., 2012; Gibbons et al., 2012). The Alzheimer's Disease Assessment Scale Cognition 13-item scale (ADAS13) and Mini-Mental State Exam (MMSE) were included to assess global cognition (Skinner et al., 2012). All the assessments were completed at baseline and 6-, 12-, 24-, 36-, 48-, and 60-month follow-ups.

2.7. Brain structures on MRI

The MRI data of brain structures can be found the ADNI dataset (https://ida.loni.usc.edu/pages/access/study). In brief, structural MRI brain scans were acquired via 1.5-T or 3.0-T MRI imaging systems with T1-weighted scan and average examination time for each person was 45 minutes. The sagittal 3D MP-RAGE sequence was used for each participant to collect two high-resolution T1-weighted MRI scans. Herein, we choose middle temporal volume, hippocampal volume and entorhinal cortex as regions of interest (ROIs) based on their established role in predicting AD progression and risk (Jack et al., 1998; Kesslak et al., 1991; Simmons et al., 2009; Velayudhan et al., 2013).

2.8. Statistical analyses

We tested demographic and diagnostic variables between SSD and healthy controls using Mann-Whitney U test (for variables with skewed distributions), Student t test (for continuous variables with normal distributions) and Chi-square tests (for categorical variables). In case of

skewed distribution (Shapiro-Wilk test > 0.05) of data (brain structures and cognitive measurement), transformation was used to approximate a normal distribution via "car" package of R software.

Multiple linear regression models were used to estimate baseline effects. And a series of linear mixed-effects models were conducted to evaluate the associations between SSD and changes in cognition and brain ROIs during the 5-year follow-up period. These models had random intercepts and slopes for time and an unstructured covariance matrix for the random effects and included the interaction between (continuous) time and SSD as predictor. In linear mixed-effects models, all outcome variables were standardized to z scores. All analyses were adjusted for age, gender, educational level, APOE4 status, clinical diagnosis of AD, type 2 diabetes mellitus (DM2), hypertension, hyperlipidemia, body mass index (BMI) and intracranial volume (for brain ROIs). In the secondary analysis, to evaluate whether the effects of SSD on brain aging outcomes were modified by baseline Aβ levels over the follow-up period, the interaction term (i.e., SSD × time × Aβ) were incorporated into linear mixed-effects models. All lower-order interactions of this 3-way interaction term were also included in the linear mixed-effects models. If significant effects of SSD were observed, we repeated these analyses by using baseline GDS scores (i.e., continuous variable) as predictor to evaluate whether magnitudes of cognitive change differed as a function of severity of baseline depressive symptoms.

We additionally conducted sensitivity analyses by classifying the participants with SSD into subgroups (i.e., SSD only and SSD plus Anxiety). Further sensitivity analyses were performed using only participants in whom NPI-Q were available (N = 524).

Bonferroni method was used to examine significance of SSD after correcting for multiple comparisons in each subgroup. P < 0.05 was considered significant in all analyses. All statistical analyses were performed using the software program (R, version3.2.3; The R Foundation).

3. Results

3.1. Participants demographics

Group characteristics and comparisons are presented in table1. There were 785 people with SSD (mean age 73.0 years, SD 7.3) and 403 without (mean age 74.5 years, SD 6.4). The classification of participants resulted in 511 Aβ-Positive (357 SSD, mean age 72.7 years, SD 7.1) and 372 Aβ-Negative (234 SSD, mean age 71.7 years, SD 7.6).

3.2. SSD and cognition

At baseline analyses, the SSD group had worse performance in MMSE scores, ADAS-cog13 scores, episodic memory and executive function among all participants (Table 1). With adjustment for all covariates, the SSD group displayed worse executive function (β = – 0.133, p = 0.006) among all participants. In the fully adjusted models, there was no significant group difference between SSD and HC for episodic memory (β = – 0.042, p > 0.05), MMSE scores (β = – 0.054, p > 0.05) and ADAS-cog13 scores (β = 0.579, p > 0.05) among all participants. In subgroup analysis, the same effects were performed among Aβ-Positive and Aβ-Negative groups (Table 1). No significant group differences were found in subgroup analysis after correction for all covariates.

In longitudinal analyses, SSD was associated with more rapid increases in ADAS-cog13 scores (β = 0.848, p < 0.001) and accelerated decline in MMSE scores (β = – 0.346, p < 0.001) among all participants during the 5-year follow-up period (Fig. 1A, B). Meanwhile, SSD was also associated with more rapid decline in episodic memory (β = – 0.049, p < 0.001) and executive function (β = – 0.045, p < 0.001) among all participants during the 5-year follow-up period (Fig. 1C, D). Subgroup analyses indicated that SSD was associated with more rapid increases in ADAS-cog13 scores (β = 1.044, p < 0.001) and accelerated reduction in MMSE scores (β = –0.458, p < 0.001) in Aβ-Positive group during the 5-year follow-up period (Fig. 1E, F). SSD was also associated with accelerated decline in episodic memory (β = –0.072, P < 0.001) and executive function (β = –0.049, p = 0.034) in the Aβ-Positive group during the 5-year follow-up period (Fig 1G, H). There were SSD-by-Aβ interactions in relation to changes in ADAS-cog13 scores (β = 0.754, p = 0.026), MMSE scores (β = – 0.327, p = 0.023) and episodic memory (β = –0.065, p = 0.004) all participants during the 5-year follow-up period (Supplementary Fig. 1A-C). When used as continuous variable, higher baseline GDS scores were associated with accelerated decline in MMSE scores and more rapid increases in ADAS-Cog13 scores among all participants and Aβ-Positive individuals during the follow-up period (Supplementary Table 1). In addition, higher GDS scores at baseline were in relation to more rapid decline in episodic memory and executive function among all participants and Aβ-Positive individuals (Supplementary Table 1). As a sensitivity analysis, the effects were stable for those only with SSD (Supplementary Table 2). For all above subgroup analyses, only the associations of SSD with executive function didn't survive the Bonferrroni adjustment.

3.3. SSD and MRI biomarkers

At baseline analyses, participants with SSD showed smaller volumes in hippocampus and entorhinal cortex without correction for covariates among all participants and Aβ-Positive group. No significant group difference was found for above ROIs after adjusting for all covariates among all participants and subgroups (Table 1).

Longitudinal analyses showed that SSD at baseline was associated with more rapid atrophy of hippocampus (β = –29.53, p = 0.001) and middle temporal gyrus (β = – 77.82, p = 0.006) among all participants during the 5-year follow-up period (Fig. 2A, B). We found no significant effect of SSD on atrophy of entorhinal cortex (β = –25.5, p = 0.08) among all participants during the 5-year follow-up period (Fig. 2C). When stratified by baseline Aβ status, SSD was associated with more rapid atrophy of hippocampus (β = –31.88, p = 0.034) and middle temporal gyrus (β = –135.7, p = 0.005) in the Aβ-Positive group during the 5-year follow-up period (Fig. 2D, E). There was no significant effect of SSD on atrophy of entorhinal cortex (β = –15.7, p = 0.07) in the Aβ-Positive group during the 5-year follow-up period (Fig. 2F). In the Aβ-Negative group, there was no significant effect of SSD on the ROIs during the 5-year follow-up period. When used as continuous variable, higher GDS scores at baseline were associated with more rapid atrophy of hippocampus (β = –6.693, p = 0.035) among all participants during the 5-year follow-up period. No significant associations of baseline GDS scores with above ROIs were found in subgroup analyses after Bonferroni correction (Supplementary Table 1). SSD didn't interact with Aβ in relation to above ROIs in longitudinal analyses. In a sensitivity analysis, the results barely changed for those only with SSD (Supplementary Table 2).

4. Discussion

The present study indicated that the presence of SSD at baseline contributed to AD-related cognitive decline and brain atrophy independently or with Aβ deposition. Moreover, there was interaction between SSD and baseline Aβ load in cognition among older people without dementia, indicating that the associations between cognition and symptoms of depression were modified by Aβ load. When treated as continuous variable, higher baseline GDS scores were associated with more rapid decline in cognition, especially in the presence of abnormal Aβ load.

The association of cognitive decline with symptoms of depression observed from our results is in line with most previous studies. As such, there's prior study showing that future cognitive performance may be

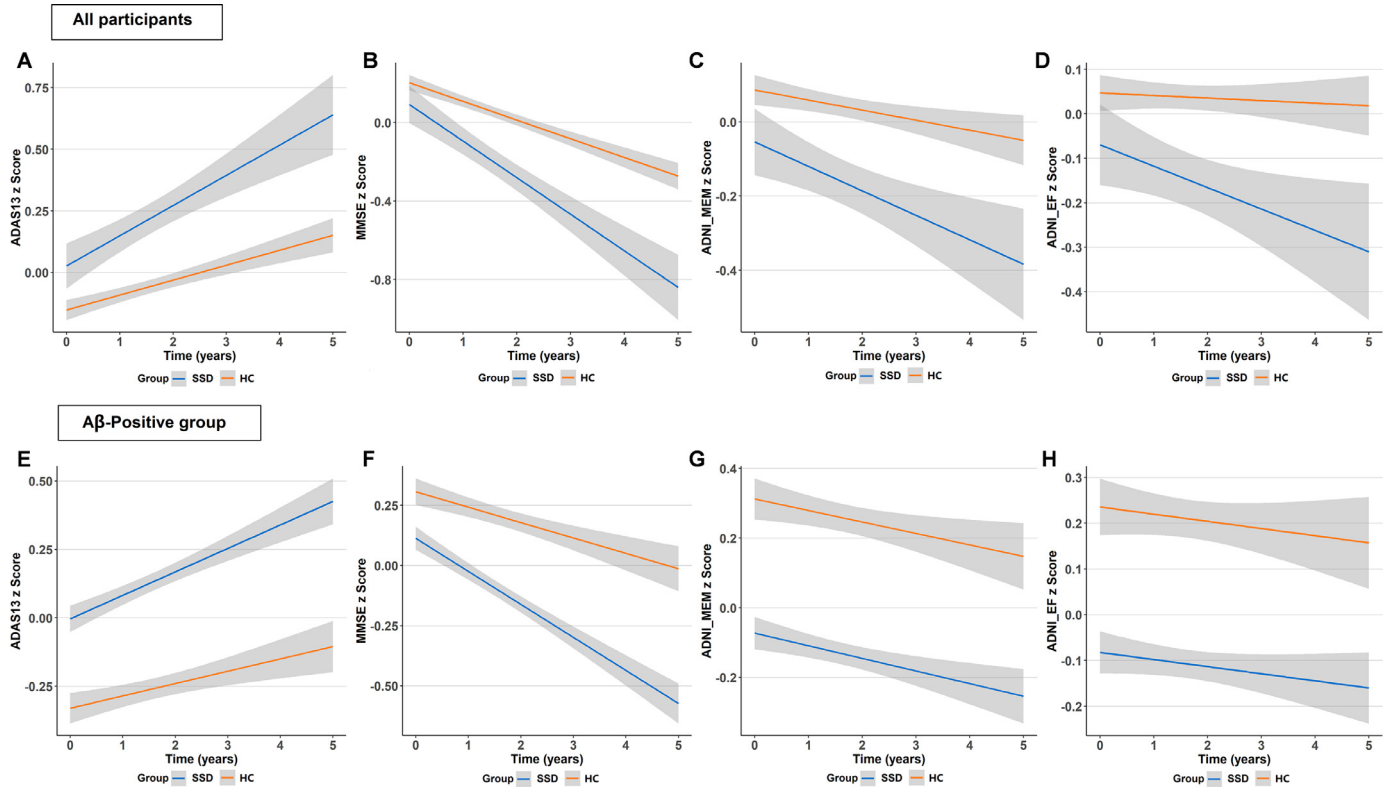

Figure 1. Effects of SSD at baseline on Alzheimer's disease-related cognition measurements in linear mixed-effects analysis among all participants and Aβ-positive group. Data from linear mixed-effects analysis adjusted for age, sex, educational level, APOE4 status, clinical diagnosis, DM2, hypertension, cardiopathy, hyperlipidemia and BMI indicating correlation of SSD with ADAS-cog13 scores (A), MMSE scores (B), episodic memory (C) and executive function (D) among all participants, and ADAS-cog13 scores (D), MMSE scores (E), episodic memory (F) and executive function (G) in Aβ-Positive group. Abbreviation: Aβ, β-amyloid; SSD, subsyndromal symptomatic depression, HC, healthy controls.

strongly predicted by the severity of baseline depressive symptom (Butters et al., 2004; Ganguli et al., 2009). Furthermore, the association between cognition and symptoms of depression in the presence of abnormal baseline amyloid was also elucidated. The finding that the interaction between Aβ and time and SSD was significant for global cognition and episodic memory indicates that Aβ-Positive status and SSD have a specifically negative effect on cognitive performance, especially in the domains of cognition that are related to hippocampus

Table 1
Participant demographics and clinical information at baseline.

	All participants (N = 1,188)			Aβ-Positive (N = 511)			Aβ-Negative (N = 372)		
	SSD (N = 785)	HC (N = 403)	p value	SSD (N = 357)	HC (N = 154)	p value	SSD (N = 234)	HC (N = 138)	p value
Age (Mean ± SD, year)	73.0 ± 7.3	74.5 ± 6.4	< 0.001	72.7 ± 7.1	75.3 ± 6.2	< 0.001	71.7 ± 7.6	72.2 ± 6.1	0.581
Gender (M/F)	440 / 345	220 / 183	0.632	204 / 153	77 / 77	0.147	120 / 114	76 / 62	0.520
Education (Mean ± SD, year)	15.9 ± 2.9	16.2 ± 2.7	0.06	16.0 ± 2.8	16.1 ± 2.7	0.727	16.1 ± 2.7	16.5 ± 2.6	0.135
APOE ε4 carrier status (+/-)	359 / 426	148 / 255	0.003	153 / 204	88 / 66	0.004	46 / 188	24 / 114	0.681
Hypertension (yes/no)	366 /419	194 / 209	0.621	164 / 193	79 / 75	0.289	118 / 116	56 / 82	0.069
Hyperlipemia (yes/no)	346 / 439	194 / 209	0.183	164 / 193	80 / 74	0.247	99 / 135	59 / 79	0.999
Cardiopathy (yes/no)	158 / 627	89 / 314	0.431	58 / 299	27 / 127	0.700	40 / 194	24 / 114	0.999
BMI (Mean ± SD, kg/m^2)	27.0 ± 4.8	27.0 ± 4.8	0.978	26.8 ± 4.3	26.6 ± 4.6	0.640	28.0 ± 4.9	28.0 ± 5.1	0.960
DM2 (yes/no)	65 / 720	25 / 378	0.200	25 / 332	10 / 144	0.999	23 / 211	7 / 131	0.118
GDS score (Mean ± SD)	2.0 ± 1.8	0 ± 0	< 0.001	2.0 ± 1.1	0 ± 0	< 0.001	2.1 ± 1.2	0 ± 0	< 0.001
Antidepressant use (yes/no)	32 / 753	9 / 394	0.002	13 /344	1 /153	0.001	2 / 232	0 / 138	0.001
CN/MCI	219 / 566	236 / 167	< 0.001	69 / 288	80 / 74	< 0.001	99 / 135	98 / 40	< 0.001
MMSE score	28.0 ± 1.8	28.5 ± 1.6	< 0.001	27.7 ± 1.9	28.3 ± 1.7	0.003	28.6 ± 1.5	28.8 ± 1.3	0.104
ADAS13 score	14.7 ± 7.1	12.1 ± 6.4	< 0.001	16.2 ± 7.2	13.1 ± 6.9	< 0.001	11.3 ± 5.5	10.1 ± 5.5	0.054
ADNI_MEM	0.4 ± 0.8	0.7 ± 0.7	< 0.001	0.2 ± 0.7	0.6 ± 0.8	< 0.001	0.7 ± 0.7	0.9 ± 0.7	0.007
ADNI_EF	0.3 ± 0.9	0.6 ± 0.9	< 0.001	0.7 ± 0.9	0.4 ± 0.9	0.036	0.6 ± 0.7	1.0 ± 0.7	< 0.001
Hippocampus (Mean ± SD, mm^3)	6594 ± 1083	7192 ± 1047	< 0.001	6841 ± 1035	7137 ± 995.4	0.005	7378 ± 1050	7448 ± 981.7	0.553
Entorhinal cortex (Mean ± SD, mm^3)	3591 ± 710.8	3706 ± 718.9	0.015	3550 ± 683.8	3686 ± 860.6	0.055	3806 ± 662.8	3815 ± 673.2	0.899
Middle temporal gyrus (Mean ± SD, mm^3)	19583 ± 2966	19997 ± 2744	0.45	19829 ± 2957	19905 ± 2586	0.800	20607 ± 2693	20537 ± 2766	0.821

Abbreviation: SSD, Subsyndromal symptomatic depression; HC, Healthy controls; BMI, Body Mass Index; DM2, Diabetes Mellitus Type 2; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Exam; ADAS13 = Alzheimer's Disease Assessment Scale Cognition 13-item scale; CN, individuals without cognitive impairment; MCI, mild cognitive impairment individuals; Aβ-Positive was defined as the concentration of Aβ42 in CSF ≤ 192pg/ml or a florbetapir standard uptake value ratio (SUVR) above 1.11 using the whole cerebellum reference region on 18F-AV-45-PET.

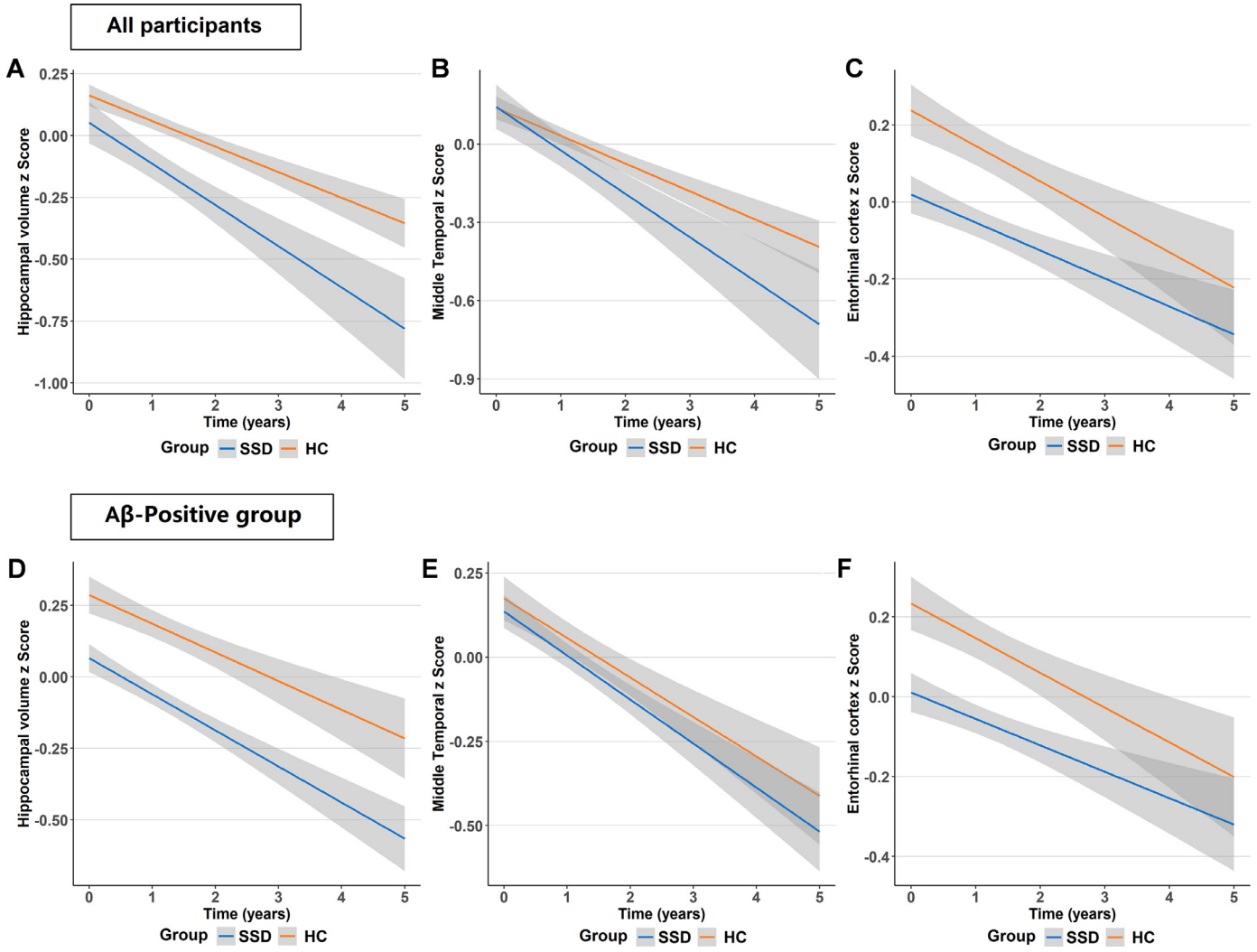

Figure 2. Effects of SSD at baseline on Alzheimer's disease-related neuroimaging markers in linear mixed-effects analysis among all participants and Aβ-positive group. Data from linear mixed-effects analysis adjusted for age, sex, educational level, APOE4 status, clinical diagnosis, DM2, hypertension, cardiopathy, hyperlipidemia, BMI and intracranial volume indicating correlation of SSD with hippocampal volume (A), middle temporal gyrus (B), and entorhinal cortex (C) among all participants, and hippocampal volume (D), middle temporal gyrus (E), and entorhinal cortex(F) in Aβ-Positive group. Abbreviation: Aβ, β-amyloid; SSD, subsyndromal symptomatic depression; HC, healthy controls.

and temporal function. The observed result is also in accordance with research of amyloid imaging showing that Aβ retention is associated with memory deterioration and pronounced in above regions (Villain et al., 2012).

There are several hypotheses that link cognitive impairment, brain atrophy and depression symptoms. The glucocorticoid cascade hypothesis suggests that elevated depressive symptoms may increase endogenous levels of glucocorticoids to exacerbate Aβ related cognitive deterioration (Butters et al., 2008). High levels of glucocorticoids may consequently damage brain regions especially the hippocampus and lead to more accelerated decline in memory or other related cognitive functions overtime (Alves et al., 2014; Sierksma et al., 2010). In addition, changes of inflammation factor and mediators may also play a very important part in cognitive decline. Prior studies have shown that both depression and dementia have high levels of pro-inflammatory cytokines (Leonard, 2007; Maes et al., 2009). Studies also have shown that depression and amyloid beta have an interaction through inflammatory-mediated pathways. Based on in vivo and in vitro studies, microglia can be activated by Aβ to release proinflammatory cytokines, and microglial activation has been observed in older adults diagnosed with mild cognitive impairment (Okello et al., 2009). Finally, it's reported that changes in brain derived neurotrophic factor (BDNF) have been also associated with both depression and cognitive impairment (Caraci et al., 2010).

Depressive symptoms were associated with cognitive decline and atrophy of hippocampus and middle temporal gyrus, which suggested that treatment of depressive symptoms may help delay or slow progressive cognitive decline. SSD interacted with baseline Aβ load in predicting longitudinal decline in cognition, and identifying these symptoms may also help manage or inform risk stratification for individuals in the phases of preclinical and prodromal AD before the antiamyloid therapies are available.

There are certain strengths and limitations in our study. Firstly, our study was based on a relatively long follow-up period and a well characterized cohort. The results of our analyses also extend prior work further elucidating the association among symptoms of depression, Aβ load and cognitive decline. Though the magnitude of our findings might be influenced by limited range of depressive symptoms, it also made it possible to explore the effect of minimal to mild depressive symptoms very common in elderly individuals. Previous study has also shown that depressive symptoms within above range have more close relation to trajectory of cognition compared to major or severe symptoms of depression. While the GDS self-report was used to evaluate depressive symptoms, the GDS is considered to have more clinical relevance

because it's similar to assessments of depression in clinical trials (Shin et al., 2019).

Despite these strengths, our study had certain limitations that should be highlighted. First, it's necessary to notice that we didn't require any specific symptoms of depression or individual items of the GDS self-report to be included or excluded from our statistical analyses for our designation of SSD because of our intention to elucidate the effects of SSD evaluated by GDS on brain aging outcomes among prodromal Alzheimer's Disease. The results scarcely changed after excluding the GDS item referring to memory complaints in sensitivity analysis. Second, we concentrated on symptoms of depression at baseline to predict cognitive decline and brain atrophy during the follow-up period. And therefore, there's possibility that the severity or range of depressive symptoms might have changed over time at follow-up evaluations. We did not exclude any participants of whom the depressive symptoms changed over the 5-year follow-up period from our study because of our initial aims to explore the effects of baseline depressive symptoms on brain aging outcomes over time. Third, our study didn't look at AD diagnosis. Although some individuals may be Aβ positive, they may not actually develop dementia. Fourth, anxiety was associated with the risk of AD and its presence is a strong predictor for future cognitive decline (Santabarbara et al., 2020; Sinoff and Werner, 2003). Given that there is an overlap and a mixed etiology between depression and anxiety in some cases, we have conducted a sensitivity analysis by classifying participants with SSD into subgroups in our study. However, we have to note that the sample of participants with assessment of anxiety symptoms was small. For some participants with SSD, the absence of assessment for anxiety symptoms is likely to limit the generalizability of our results.

5. Conclusion

Our findings suggested that cognitive healthy people with both SSD and a high level of Aβ deposition may have higher risk of cognitive deterioration and brain atrophy. In summary, these findings suggested that, among elderly individuals without dementia, especially those in the presence abnormal Aβ load, treatment of depressive symptoms may help delay progressive cognitive decline. Given that symptoms of depression (especially minimal to mild range) remain amenable to treatment, identifying these symptoms may also help manage or inform risk stratification for individuals in the phases of preclinical and prodromal AD before the antiamyloid therapies are available.

Author statement

Contributions: Prof. Yu: conceptualization and design of the study, analysis and interpretation of data and revision of the manuscript. Zhao Zhang: collection and analysis of the data, drafting and revision of the manuscript, and prepared all the figures. WEI-FENG, Xue-Ning Shen, Ya-Hui Ma, Ke-Liang Chen, Qiang Dong: revision of the manuscript. Prof. Lan Tan: design and conceptualization of the study, revision of the manuscript.

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Declaration of Competing Interest

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Supplementary materials

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