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Research paper

Hippocampal volume maximally modulates the relationship between subsyndromal symptomatic depression and cognitive impairment in non-demented older adults

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ABSTRACT

Background: Subsyndromal symptomatic depression (SSD) is associated with an elevated risk of cognitive impairment in non-demented older adults. Given that hippocampal and middle temporal gyrus atrophy have been shown to cause SSD, our study aimed to investigate the effect of hippocampal volume on the association between SSD and cognitive impairment.

Methods: 338 non-demented older adults from the ADNI (Alzheimer's Disease Neuroimaging Initiative) cohort who underwent cognitive assessments, questionnaires on depressive symptoms and MRI brain were studied. SSD group is defined as a score of 1–5 based on Geriatric Depression Scale scores. We conducted causal mediation analyses to investigate the effect of hippocampal volume on cognitive performance cross-sectionally.

Results: The SSD group displayed lower left and right hippocampal volume ($p<0.01$) than the non-SSD group. SSD was linked to poorer cognition and smaller hippocampal volume. We found that hippocampal volume partially mediated the effect of SSD on cognitive performance including the global cognition and the cognitive section of Alzheimer's Disease Assessment Scale, with mediation percentages ranging from 6.45 % to 30.46 %. In addition, we found that the thickness of the left middle temporal, right entorhinal and right fusiform gyrus, brain regions linked to AD, mediate the relationship between SSD and cognition with mediation percentages ranging from 8.67 % to 21.44 %.

Limitations: Our article didn't differentiate between mild cognitive impairment and normal population.

Conclusion: The associations of SSD and cognitive impairment are linked to alterations in Alzheimer's Disease related brain regions.

1. Introduction

Older adults who experience depressive symptoms or have major depression are at a higher risk of cognitive deterioration (Wilson et al., 2002). Depressive symptoms are also associated with faster deterioration of cognitive abilities in older adults with Alzheimer's Disease (AD)

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[2] 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 provided 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.

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(Rapp et al., 2008; Rapp et al., 2011). Hence, depressive symptoms are regarded as a significant risk factor and early neurologic manifestation of AD (Becker et al., 2009; Ganguli et al., 2006; J.Q. Li et al., 2016).

The clinical manifestation of depressive symptoms varies widely from subsyndromal depression (SSD) to major depression. SSD is a clinical construct that describes individuals with some clinical symptoms of depression not meeting the diagnostic criteria of major depression but having serious occupational function decline and social function impairment (Lyness et al., 2009; Rodríguez et al., 2012). Although SSD is prevalent in the elderly population, SSD is often overlooked as an at-risk clinical entity for cognitive impairment. In this regard, existing studies have consistently shown that people with SSD have deficits in cognitive activities such as emotion processing (Dedovic et al., 2016; H. Li et al., 2016; Woo et al., 2009; Yang et al., 2020; Zhang et al., 2022), reward processing (Falconier et al., 2015), self-consciousness processing (Dedovic et al., 2014; Shiota et al., 2017), and thinking activities (Hinton et al., 2014). SSD has also been linked to longitudinal decline in cognitive performance (Shimada et al., 2014).

Age-related brain structural changes, particularly hippocampal atrophy may influence the link between depression and cognition. For instance, individuals with lower cognitive function or signs of depression showed smaller hippocampus (Boccia et al., 2015; Steffens et al., 2000; Zacková et al., 2021). Right hippocampus volume is shown to be diminished in older persons with depression (Bell-McGinty et al., 2002) and depressed older people with hippocampus volume reduction are more likely to experience deterioration in cognition (Steffens et al., 2011). Alterations in hippocampal neurogenesis can mediate the effects of antidepressants (Schmidt and Duman, 2007), and intensive drug therapy in patients with depressive episodes can prevent hippocampal deterioration (Hviid et al., 2010). Furthermore, emerging studies are showing that people with SSD have alterations in brain activation and brain connectivity mainly in the frontal lobe, parietal lobe, hippocampus, amygdala (Li et al., 2017), cingulate gyrus, pontine gyrus, striatum and insula. Atrophy of the hippocampal region and middle temporal gyrus are also significantly accelerated in individuals with SSD (Yesavage et al., 1982; Zhang et al., 2020). However, the influence of the morphological alterations in brain regions, such as hippocampal volume on the associations of SSD with cognitive impairment remains unclear.

Here, in a cross-sectional observation of non-demented adults stratified into SSD and non-SSD groups, we aim to investigate the associations of depressive symptoms with cognitive performance and the hippocampal volume among SSD. Moreover, we will test the hypothesis that the effects of depressive symptoms on cognitive performance are mediated by hippocampal volume. Findings of this study will provide insights into the mechanisms underlying cognitive impairment in individuals with SSD.

2. Methods and materials

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. 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 AD. The institutional review boards of all participating centers granted approval to the ADNI study. Additional details can be acquired through the website http://www.adni-info.org/ or by referring to previous reports.

2.1. Participants

This study recruited participants from ADNI-1, ADNI-2, ADNI-GO and ADNI-3 cohorts. We selected non-demented participants who underwent cross-sectional cognitive assessments, Geriatric Depression Scale (GDS) scores and MRI brain scan. We excluded participants who had insufficient data on sociodemographic characteristics (age, sex, education, APOEε4 status), regional MRI brain morphological parameters (posterior cingulate, temporal lobe, parahippocampus, internal olfactory cortex, precuneus) and cognitive scores, individuals with major depression or significant symptoms of depression (GDS score > 5). Finally, we included 338 older non-demented adults (131 cognitively normal (CN) and 207 MCI) in our study. More detailed information on CN and MCI can be found on the ADNI database (adni.loni.usc.edu).

2.2. Depression scale measurement

We used the GDS-15 to evaluate the depressive symptoms of participants (Yesavage et al., 1982). GDS total scores vary from 0 to 15, higher GDS scores indicate higher depressive symptoms. Participants with SSD were assigned a score of 1–5 and healthy controls a score of 0 as validated in previous studies (Bertens et al., 2017; Zhang et al., 2020). Using this cut-off, we stratified our participants into SSD ($1 \leq$ GDS score ≤ 5) and non-SSD (GDS score $= 0$).

2.3. Cognitive measures

The Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), the CDR Sum of Boxes (CDR-SB), Montreal Cognitive Assessment (MoCA), Functional Assessment Questionnaire (FAQ) were utilized in assessing global cognition. The ADNI Memory (ADNI-MEM) and the Rey Auditory Verbal Learning Test (RAVLT) were included to describe memory function. RAVLT which included RAVLT immediate (the sum of scores from five first trials [trials1–5]), RAVLT Learning (the score of Trial 5 minus the score of Trial 1), RAVLT forgetting (the score of Trial 5 minus score of the delayed recall) and RAVLT percent forgetting (RAVLT forgetting divided by the score of Trial 5). For executive function, we used the ADNI Executive Function (ADNI-EF) and the Everyday Cognition (ECog) questionnaire (EcogPtTotal) for the interview. To obtain further details, please visit https://adni.loni.usc.edu/methods/.

2.4. MRI imaging

The ADNI database (http://adni.loni.usc.edu/) contains MRI data on brain structures. T1-weighted scans were carried out using either 3.0-T MRI imaging system. These MRI images were automatically quantified using FreeSurfer. MRI image processing was completed by ADNI staff. We selected the posterior cingulate, temporal lobe, parahippocampus, internal olfactory cortex, and precuneus as regions of interest (ROIs) as these ROIs are closely associated with AD (Apostolova and Thompson, 2008; Petersen and Jack Jr., 2009).

2.5. Data analysis

The data was analyzed using SPSS 25.0 statistical software and R software version 4.4.0. The numerical variables were expressed as mean $\pm$ standard deviation, and two-sample *t*-test was used for comparison between groups. The categorical variables were expressed as percentage (%), and chi-square ($\chi 2$) test was used for comparison between groups. When the variance of each group did not satisfy normality or chi-square ($\chi 2$), Wilcoxon rank sum test was used. Analysis of covariance was used to adjust for discrepancies in brain area and cognitive characteristics, adjusting for age, gender, education, and APOEε4 status. In addition, estimated total intracranial volume (ICV) as a covariate was added for correction when comparing brain area. Statistical significance was considered at $P < 0.05$.

Mediation analysis was performed among SSD and Non-SSD group together. First, we examined the independent associations of GDS scores with cognition and hippocampal volume. Linear regression was used to

analyze the cross-sectional relationship of GDS (independent variable) with hippocampal volume and overall cognition (continuous variable, dependent variable) separately. Second, we aimed to examine the mediating effect of hippocampal volume on the association between GDS and cognition. The mediation model was established when the following conditions were met: 1) GDS were significantly related to brain region morphological parameters of brain regions. 2) GDS was significantly associated with cognitive measures. 3) Brain region morphological parameters of brain regions were significantly related to cognitive measures. 4) The association between GDS and cognition was weakened with the inclusion of brain regions in the regression model. Furthermore, the estimation of the attenuation or indirect effect was carried out, and its significance was ascertained through 10,000 bootstrapped iterations, wherein each model path was meticulously controlled for age, gender, education, APOEε4 status, and ICV.

3. Results

3.1. Participant characteristics

A total of 338 non-demented older adults (131 CN and 207 MCI) were included in this study. A total of 228 participants were in the SSD group and 110 in the non-SSD group. There were no statistically significant differences in mean age, gender, education, APOEε4 status, and ICV between the SSD and non-SSD groups ($P > 0.05$), Table 1. The SSD group performed worse in the ADAS, ADNI-MEM, ADNI-EF, CDR-SB, EcogPtTotal, FAQ, MoCA and RAVLT immediate scores compared to the non-SSD group ($P < 0.05$), whereas there was no statistically significant difference in MMSE, RAVLT forgetting, RAVLT learning, and RAVLT perc forgetting scores between the SSD group and the non-SSD group ($P > 0.05$) (Table 2).

3.2. Morphological parameter analysis

We found differences in the morphology of brain regions between the SSD and non-SSD groups, with bilateral hippocampal volumes being smaller in the SSD group than in the non-SSD group (Table 3). In addition, we also found differences in the surface of left fusiform, left parahippocampus, and right entorhinal, the cortical thickness average of right entorhinal, cortical thickness standard deviation of bilateral parahippocampus, left entorhinal between the SSD and non-SSD groups ($p < 0.05$). However, after FDR correction, the differences in left fusiform, bilateral parahippocampus and entorhinal between the SSD and non-SSD groups were not significant (Additional Tables 2–4).

3.3. Causal mediation analysis

In the first regression, GDS was found to be significantly associated with smaller volumes of the left hippocampus ($p<0.01$) and right hippocampus ($p = 0.04$). The second regression revealed a significant association between GDS and poorer cognition, as measured by MMSE ($p<0.01$), ADAS11 ($p<0.01$), ADAS13 ($p<0.01$), ADASQ4 ($p<0.01$), ADNI-MEM ($p<0.01$), ADNI-EF ($p<0.01$). Finally, the third equation showed that the effect of depressive symptoms on global cognition remained, but was attenuated when hippocampal volume was included in the model. Overall, the relationship between depressive symptoms and cognitive impairment was partially moderated by the volumes of the left and right hippocampus. Additionally, similar results were observed for memory and executive function, with a modulation percentage ranging from 6.45 % to 21.75 % ($p < 0.05$), Fig. 1. At the same time, in other cognitive score (CDR-SB, EcogPtTotal, FAQ, MoCA and RAVLT immediate), we also came to mediation effects of the hippocampus, ranging from 3.54 % to 20.78 % (Additional Fig. 1). Moreover, we found that the left hippocampus had a higher proportion of regulation compared to the right hippocampus in all model, indicating that the left hippocampus plays a more prominent role in the association of SSD with cognitive impairment.

In addition to the hippocampus, we investigated whether temporal lobe thickness is involved in modulating the relationship between depressive symptoms and cognition given that the temporal lobe is closely associated with AD. Similar results were obtained in the domains of global cognition and other cognitive domains including memory and executive function. Specifically, we found that the left middle temporal thickness (proportion = 12.24 %–15.45 %), cortical thickness average of right entorhinal (proportion = 8.67 %–21.44 %), and right fusiform gyrus thickness (proportion = 9.69 %–14.21 %) were involved in the modulation of depressive symptoms on cognition (Fig. 2). All of above ROIs regulate a smaller proportion than the hippocampal volume. Taking CDR-SB, EcogPtTotal, FAQ, MoCA and RAVLT immediate scores as cognitive outcomes respectively, we also came to mediation effects of ROIs, with proportion ranging from 3.88 % to 13.58 % (Additional Fig. 2).

Given the age has been significantly associated with gray matter volume in the hippocampus, especially in older people. A subgroup analysis was conducted in 237 people (83 non-SSD and 154 SSD) aged 65–80. There was no statistically significant difference in age between the two samples ($p = 0.254$). The mediation analysis shows that the

Table 1
The demographic characteristics of participants.

	Non-SSD (N = 110)	SSD (N = 228)	*P* value
Age, years	72.88 ± 6.83	71.32 ± 7.21	0.06
Female, n (%)	48 (43.60 %)	115 (50.40 %)	0.24
Years of education	16.54 ± 2.57	16.45 ± 2.55	0.78
APOE4(+/+), n (%)	46 (41.82 %)	96 (42.11 %)	0.96
Estimated total intracranial volume (ICV)	1,512,492 ± 169,795.11	1,505,615.24 ± 159,752.21	0.72

Abbreviation: SSD, Subsyndromal symptomatic depression; APOE, Apolipoprotein E; Results are mean ± (SD). *P* value assessed using two-tailed Student *t*-test for age. Female and APOE 4 were performed by chi-square ($\chi 2$) test. Mann-Whitney test was used for years of education and ICV. Statistical significance was considered at $P < 0.05$.

Table 2
The neurocognitive measurement characteristics of participants.

	Non-SSD (N = 110)	SSD (N = 228)	P value
MMSE Score	28.69 ± 1.40	28.39 ± 1.64	0.05
ADAS-Cog11	6.75 ± 3.63	8.44 ± 4.76	<0.01**
ADAS-Cog13	10.75 ± 6.12	13.66 ± 7.13	<0.01**
ADASQ4 Score	3.49 ± 2.54	4.61 ± 2.60	<0.01**
ADNI-MEM	0.83 ± 0.76	0.53 ± 0.73	<0.01**
ADNI-EF	0.68 ± 0.90	0.43 ± 0.86	<0.01**
GDS	0.00	2.09 ± 1.16	<0.01**
CDR-SB	0.62 ± 0.87	1.09 ± 1.02	<0.01**
EcogPtTotal	1.39 ± 0.34	1.77 ± 0.53	<0.01**
FAQ	0.92 ± 1.90	2.20 ± 3.62	<0.01**
MoCA	25.12 ± 3.27	24.09 ± 3.14	<0.01**
RAVLT forgetting	4.02 ± 2.67	4.39 ± 2.61	0.14
RAVLT immediate	42.05 ± 12.11	39.28 ± 11.46	<0.01**
RAVLT learning	5.29 ± 2.47	5.25 ± 2.59	0.72
RAVLT-perc-forgetting	44.43 ± 32.11	49.18 ± 31.61	0.08

Data were presented as mean ± standard deviation. Statistical significance was considered at $P < 0.05$. *P* values were adjusted by age, gender, years of education, APOE ε4 status appropriately. Abbreviation: MMSE: Mini-mental state examination, ADASCog11 or 13: Alzheimer disease assessment scale-11 or 13-item subscale, ADASQ4: ADAS Delayed Word Recall, ADNI-MEM, ADNI-Memory summary score; ADNI-EF: ADNI-Executive function summary score, GDS: Geriatric Depression Scale, CDR-SB: Clinical dementia rating scale-sum of boxes, ECogPtTotal: the Everyday Cognition questionnaire; FAQ: Functional assessment questionnaire; MoCA: Montreal cognitive assessment; RAVLT: Rey Auditory Verbal Learning Test. RAVLT which included RAVLT immediate, RAVLT Learning, RAVLT forgetting and RAVLT percent forgetting.

** P<0.01.

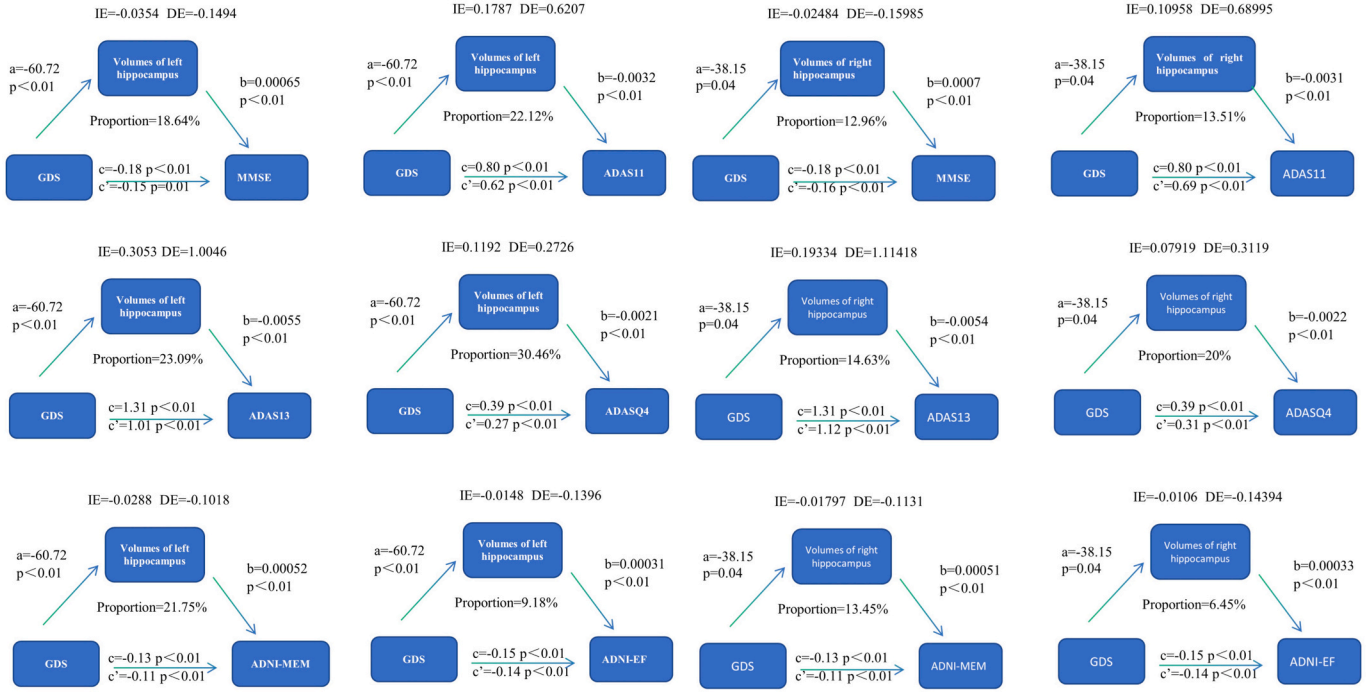

Fig. 1. Mediation analyses with Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS) as cognitive outcome. The ADNI Memory (ADNI-MEM) was included to describe memory function. The ADNI Executive Function (ADNI-EF) was included to describe executive function. In ADNI (Alzheimer's Disease Neuroimaging Initiative), the relationship between Subsyndromal symptomatic depression assessed by the Geriatric Depression Scale (GDS) scores and cognitive impairment was mediated by Volumes of left and right hippocampus. Proportion was adjusted by age, gender, years of education, APOEε4 status, estimated total intracranial volume appropriately. IE, indirect effect. DE, direct effect.

Fig. 2. Mediation analyses with Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS) as cognitive outcome. The ADNI Memory (ADNI-MEM) was included to describe memory function. The ADNI Executive Function (ADNI-EF) was included to describe executive function. In ADNI (Alzheimer's Disease Neuroimaging Initiative), the relationship between Subsyndromal symptomatic depression assessed by the Geriatric Depression Scale (GDS) scores and cognitive impairment was mediated by cortical thickness average of left middle temporal, right entorhinal, right fusiform. Proportion was adjusted by age, gender, years of education, APOEε4 status, estimated total intracranial volume appropriately. IE, indirect effect. DE, direct effect.

mediation effects in hippocampus are still valid, with mediation percentages ranging from 9.62 % to 26.78 % (Additional Fig. 3).

When stratified all individuals into MCI or CN groups, the mediation effects were not established due to criteria were not simultaneously satisfied (Additional Figs. 4 and 5). That probably due to the clinical diagnosis (MCI or CN) were intimate to cognitive scores, stratifying participants into groups according to diagnosis weaken the relationship between GDS and cognitive scores.

4. Discussion

Our study showed that SSD in non-demented older adults was significantly associated with worse global cognitive performance and memory and executive function cognitive domains compared to non-SSD. SSD in non-demented older adults is also associated with lower hippocampal volume compared to non-SSD. Furthermore, the associations of SSD and cognitive impairment were partially mediated by hippocampal atrophy. These findings provide further insights into the mechanisms underlying the association of depressive symptoms and

Table 3
The MRI imaging characteristics of participants.

Brain region	Non-SSD (N = 110)	SSD (N = 228)	P value	PFDR
Volumes of right hippocampus	3781.4 ± 511	3611 ± 539	0.0000806**	0.0059644**
Volumes of left hippocampus	3695.6 ± 561	3529 ± 548	0.000395**	0.0146150*
Volume of left posterior cingulate	2990.9 ± 459.3	2981.2 ± 452.8	0.8818	0.9321886
Surface area of left posterior cingulate	1095.9 ± 170.6	1098.3 ± 162.7	0.83509	0.9119521
Cortical thickness average of left posterior cingulate	2.52 ± 0.16	2.51 ± 0.17	0.4256	0.8512
Cortical thickness standard deviation of left posterior cingulate	0.67 ± 0.09	0.66 ± 0.09	0.46209	0.8677097
Volume of right posterior cingulate	2978.67 ± 494.01	2935.79 ± 449.49	0.251772	0.776297
Surface area of right posterior cingulate	1119.87 ± 176.06	1103.14 ± 174.17	0.2111	0.7423545

More detailed data can be found in the Appendix.
Data were presented as mean ± standard deviation. Statistical significance was considered at $P < 0.05$. P values were adjusted by age, gender, years of education, APOEε4 status, estimated total intracranial volume appropriately. PFDR is the result of FDR correction.
** $P<0.01$.
* $P<0.05$.

cognition. Hence, our findings suggest that the deleterious effects on cognitive impairment may be amplified by the vicious cycle formed by depressive symptoms and reduced hippocampal volume.

Our causal mediation analysis findings are consistent with existing literature. A longitudinal study showed that the synergistic effect of depressive symptoms and smaller hippocampal volume in MCI population accelerated the conversion from MCI to AD (Chung et al., 2016). Zhao Zhang et al. found that the hippocampus and internal olfactory cortex of individuals with SSD exhibited smaller volumes (Zhang et al., 2020). Saczynski et al. conducted an epidemiologic study of 136 participants with AD and depressive symptoms and found that depression was associated with cognitive decline and accelerated neuropathologic changes in the hippocampus (Saczynski et al., 2010). Participants with SSD also exhibited glucose hypometabolism in the hippocampus, amygdala, precuneus/posterior cingulate cortex, medial and dorsolateral prefrontal cortex, insula, and temporoparietal cortex (Touron et al., 2022). Grace et al. found that depressive symptoms were associated with greater atrophy in AD-related areas, the increased cognitive decline, and a higher rate of conversion to AD and that MCI in the depressive symptoms predicted more severe atrophy in AD-related regions (Lee et al., 2012). Although existing studies have demonstrated a strong relationship between SSD and cognition and brain morphology, the specific mediating effects of these three components have not been clearly reported. Our study builds on the current findings by demonstrating the specific mediating effects of hippocampal volume on the associations of subclinical depressive symptoms on cognition.

The mechanisms by which subclinical depressive symptoms in SSD modulate cognition through hippocampal volume remain unclear. Several biological mechanisms have been postulated to explain the impact of depressive symptoms on hippocampal volume. First, persistent chronic stress is associated with depressive states, leading to impaired microglia function and inhibition of hippocampal neurogenesis (Yin et al., 2019), and the effects of chronic stress are, at least in part, selective for the hippocampus (Bremner et al., 2000; Sheline et al., 1996). Second, an elevation in depressive symptoms could potentially heighten the levels of endogenous glucocorticoids according to the glucocorticoid cascade hypothesis. Consequently, this can aggravate the cognitive deterioration associated with Aβ (Butters et al., 2008). Excessive glucocorticoid levels can cause harm to specific areas of the brain, notably the hippocampus, resulting in a rapid deterioration of memory or other associated cognitive abilities (Alves et al., 2014; Sierksma et al., 2010). Therefore, the present study supports the idea that a smaller hippocampus may produce susceptibility or vulnerability to depression.

There are limitations to this study. First, the ADNI study participants who were recruited from volunteers may limit the generalization of our findings to clinic patients. It is imperative to conduct further extensive longitudinal studies within the clinic population to validate our findings. Second, the study sample was limited to those with the mildest depressive symptoms. Given the low severity of the condition, the magnitude of the impact of depressive symptoms may have been underestimated. Third, to maximize sample size, our analysis included both CN and MCI populations, but this may introduce bias due to population heterogeneity. For example, our study found that the left hippocampal volume was moderated proportionally more than the right hippocampus in all cases, but this result needs to be interpreted with caution. Previous studies have shown that the left and right hippocampus play different roles in CN and MCI subgroups. In the MCI subgroup, smaller hippocampal volume bilaterally was associated with poorer memory retention, whereas the left (rather than the right) hippocampus was associated with poorer encoding, and that the left hippocampal body volume mediated the relationship between MCI status and verbal encoding (Boccia et al., 2015; Du et al., 2022). Future studies are still needed to determine the mediation effects in healthy individuals and MCI individuals, respectively. The current research results will further promote in-depth exploration of this issue.

5. Conclusion

Our findings suggest that hippocampal volume changes may partially modulate the associations of SSD and cognitive impairment. The associations of SSD and cognitive impairment are linked to alterations in AD related brain regions.

Abbreviations

SSD	Subsyndromal symptomatic depression
AD	Alzheimer's Disease
ADNI	Alzheimer's disease neuroimaging initiative
MRI	Magnetic resonance imaging
GDS	Geriatric depression scale
PET	Positron emission tomography
MCI	Mild cognitive impairment
CN	Cognitively normal
MMSE	The mini-mental state examination
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
CDR-SB	The CDR sum of boxes
MoCA	Montreal cognitive assessment
FAQ	Functional assessment questionnaire
ADNI-MEM	The ADNI memory
RAVLT	The Rey Auditory Verbal Learning Test
ADNI-EF	The ADNI executive function
EcogPtTotal	The Everyday Cognition questionnaire
ROIs	Regions of interest regions
ICV	Estimated total intracranial volume

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Ethics approval and consent to participate

Ethics approval and consent to participate is not applicable to this article as no human participants, or human tissue were involved in this study.

Consent for publication

Consent for publication is not applicable to this article as no personal data were contained.

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CRediT authorship contribution statement

Chenxi Jing: Writing – original draft, Investigation, Data curation. **Min Kong:** Writing – review & editing. **Kok Pin Ng:** Writing – review & editing. **Lijuan Xu:** Validation. **Guozhao Ma:** Validation. **Maowen Ba:** Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare they have no competing interests.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

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