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Anxiety correlates with cortical surface area in subjective cognitive decline: APOE ε4 carriers versus APOE ε4 non-carriers

Yu Sun[1†], Xiaoni Wang[1†], Yinshan Wang[2†], Haoming Dong[2], Jie Lu[3], Tohar Scheininger[4], Michael Ewers[5], Frank Jessen[6], Xi-Nian Zuo[2] and Ying Han[1,7,8,9*]

Abstract

Background: Subjective cognitive decline (SCD) is characterized by self-reported cognitive deficits without measurable cognitive impairment. It has been suggested that individuals with SCD exhibited brain structural alterations in widespread cortical thinning or gray matter loss in the medial temporal and frontotemporal regions. Apolipoprotein E (*APOE*) ε4 allele is thought to be a genetic marker associated with risk of SCD. Neuropsychiatric symptoms may provide insight in detecting higher-risk elders for early Alzheimer's disease as well. Therefore, we aim to explore the characteristics of brain morphology in SCD and to determine whether it is influenced by *APOE* ε4 as well as neuropsychiatric symptoms in SCD.

Methods: A total of 138 cognitively normal older individuals from the SILCODE cohort underwent a clinical interview, neuropsychological assessments, a blood test, and MRI. A two-sample *t*-test was used to examine the cortex volume and bilateral cortical surface area alterations between SCD (n = 65) and controls (n = 73). A general linear model analysis was used to test for both main and interaction effects of clinical phenotype (SCD vs. controls) and *APOE* on global and regional cortex volume and bilateral cortical surface area and thickness. A multiple linear regression analysis was conducted to determine the effects of the *APOE* genotype on the relationships between morphometric features and neuropsychiatric symptoms in SCD.

Results: Compared with controls, individuals with SCD showed decreased total cortical volumes and cortical surface area. SCD *APOE* ε4 carriers showed additive reduction in the right cortical surface area. The evaluation scores of anxiety symptoms were negatively associated with the right cortical surface area in SCD *APOE* 4 non-carriers.

Conclusions: Individuals with SCD had an altered cortical surface area, and *APOE* genotype and anxiety symptoms are modified factors on the cortical surface area decrease in SCD.

Trial registration: ClinicalTrials.gov (Identifier: NCT03370744). Registered 15 March 2017.

Keywords: Subjective cognitive decline, Apolipoprotein E, Anxiety, Cortical morphometry, Alzheimer's disease

* Correspondence: hanying@xwh.ccmu.edu.cn
†Yu Sun, Xiaoni Wang and Yinshan Wang contributed equally to this work.
[1]Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China
[7]National Clinical Research Center for Geriatric Disorders, Beijing, China
Full list of author information is available at the end of the article

Background

Subjective cognitive decline (SCD) is a clinical state characterized by subjective cognitive deficits without measurable cognitive impairment. Individuals with SCD may show a higher risk for biomarker patterns indicative of Alzheimer's disease (AD) pathology, suggesting that SCD are at an increased risk for progressing to mild cognitive impairment (MCI) or AD [1–4]. Indeed, individuals with SCD constitute a heterogeneous population. To identify the specific characteristics of SCD that are associated with an increased likelihood of AD with affordable and easily accessible measures could help imply appropriate candidates for early detection in AD.

Previous studies have identified that individuals with SCD showed structural gray matter volume reductions and cortical thinning in the bilateral entorhinal cortex [5], medial temporal, and frontotemporal regions [6] compared to cognitively normal elders without cognitive complaints. While particular regions of the brain may be involved in the underlying pathology of AD, some abnormalities may also be present in a widespread form, thus producing global alterations to brain structure at a very early stage. SCD has known associations with an AD-like pattern of gray matter atrophy [7], and the widespread cortical thinning is associated with faster subsequent decline in memory [8]. Many studies have examined the brain volumetric and thickness measures in SCD; there is a scarcity of research investigating cortical surface area, an increasingly used brain morphology metric, which is ontogenetically and phylogenetically distinct from cortical thickness [9]. The cortical surface area is determined by symmetrical division of progenitor cells from the ventricular and subventricular zones of cortical layers, while the cortical thickness is formed by the asymmetrical division of radial glia [10]. Recent research has demonstrated that surface-based structure analysis may offer stronger statistical power than volume-based analysis in capturing subtle structural alterations as well as the effect of apolipoprotein E (*APOE*) genotype [11, 12]. Our previous work using combined resting-state functional and structural MR have found no gray matter differences in SCD compared to controls [13]. Thus, in this study, we employed surface-based analysis to detect cortical morphology which would be better suitable to manifest the subtle structural changes under early stages.

APOE ε4 allele is a well-established genetic risk factor for progression of sporadic AD, and influence of *APOE* genotype in SCD has aroused growing interests [14, 15]. Longitudinal studies have demonstrated that both memory complaints and *APOE* ε4 allele predict clinical cognitive decline in cognitively intact elderly individuals and additive effects were shown in individuals with both factors [16]. Recent meta-analysis indicated *APOE* ε4 was significantly associated with risk of having SCD in cognitively normal subjects as well as developing to AD in SCD [17]. Studies have found the significant interaction of SCD and *APOE* ε4, in which SCD *APOE* ε4 carriers performed worse on the episodic memory and showed smaller left hippocampal volumes [18], while other studies have not observed the differences associated with *APOE* ε4 statue in glucose metabolism and medial temporal lobe atrophy in SCD [19]. Thus, the *APOE* ε4 genetic effect on brain neurodegeneration as early as in SCD population remains ambiguous.

Another emerging line of research focusing on the association between neuropsychiatric symptoms (such as symptoms of depression and anxiety) and AD pathophysiologic abnormalities has suggested subtle neuropsychiatric symptoms as man289(c)9/17(s)ta(ns)17(ti)14(o)15(ms)4280(o)11(n)-392

de-noising, (2) rough inhomogeneity correction, (3) align image into MNI space, (4) inhomogeneity correction, (5) intensity normalization, (6) non-local intracranial cavity extraction [33], (7) gray matter/white matter segmentation,

Table 1 Subject demographics and neuropsychological assessments

	SCD (n = 65)	NC (n = 73)	P value
Age (years)	65.85 (4.85)	64.55 (5.52)	.147
Education	11.86 (2.70)	11.68 (3.31)	.734
Gender (male/female)	23/42	38/35	.138
APOE ε4 (+/−)[a]	16/48	14/56	.443
MMSE	28.65 (1.23)	28.79 (1.38)	.866
MoCA-B	25.25 (2.36)	25.79 (2.48)	.338
AVLT-IR	6.50 (1.13)	6.66 (1.68)	.432
AVLT-DR	6.57 (1.84)	6.95 (2.20)	.166
AVLT-R	21.95 (1.74)	22.56 (1.46)	.005
STT-A	63.49 (16.42)	64.56 (22.94)	.112
STT-B	143.85 (37.44)	139.22 (37.24)	.913
AFT	17.88 (4.28)	18.81 (4.60)	.232
BNT	24.74 (2.45)	25.26 (3.14)	.396
GDS	3.35 (3.16)	1.89 (1.80)	.382
HAMD	5.66 (4.26)	2.51 (2.64)	< .001
HAMA	6.34 (4.70)	2.65 (2.43)	< .001

apolipoprotein E, Mini-Mental State Examination, Montreal Cognitive Assessment Basic Version, Auditory Verbal Learning Test-immediate recall, Auditory Verbal Learning Test-delay recall, Auditory Verbal Learning Test-recognition, Shape Trails Test Part A, Shape Trails Test Parts B, semantic fluency (animals), Boston Naming Test, Geriatric Depression Scale, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale

[a] genotype results were included in SCD subjects (= 64) and controls (= 70)

Between-group comparisons of morphometric features on networks

There were no significant differences (Bonferroni corrected) of surface area and cortical volume in the visual, somatomotor, dorsal attention, ventral attention, limic, frontoparietal, and default networks between the SCD and control groups. The differences of cortical thickness and surface area in the frontal lobe, parietal lobe, temporal lobe, occipital lobe, cingulate, parahippocampal gyrus, and insula, as well as in bilateral posterior cingulated cortex (PCC), left prefrontal cortex (PFC), right medial PFC, right ventral PFC, parahippocampal cortex, bilateral temporal regions, and bilateral parietal regions within default mode, were not significant after Bonferroni correction.

Relationship between cortical structural measures and neuropsychological variables

In the SCD group, there was a significant negative correlation between the HAMA and right hemisphere surface area (r = − 0.328, P = .0088; Fig. 2a). Moreover, the negative correlation between the HAMA and surface area was significant in non-carriers in the SCD group (r = − 0.350, P = .016; Fig. 2b). The correlation was reanalyzed after removing the two extreme HAMA score (> 20) values; however, the significant negative correlation between the HAMA and surface area in the right hemisphere remained essentially unchanged (r = − 0.289, P = .024). Both correlations between the HAMD and recognition scores and surface area were not significant. There was no significant correlation between the HAMA and surface area in controls (r = − 0.165, P = .181).

Discussion

In line with previous literature [5, 39, 40], this study data indicated decreased cortical volume and surface area in the SCD group as compared to controls; however, there were no significant differences in structural alterations based on functional cortical networks. This suggests that the changes in global cortices in individuals with SCD were attributed to entire networks extensively, which may be related to intact cognitive performance. Cognitive complaints and *APOE* ε4 may have addictive effects on cortical surface area decline (P = .086; Table 3). Notably, anxiety scores were higher in SCD individuals and negatively correlated with surface area significantly in SCD *APOE* ε4 non-carriers.

Elevated anxiety and depression scores were found in the SCD group as compared to normal controls, which is similar with previous studies [21, 41]. It is possible

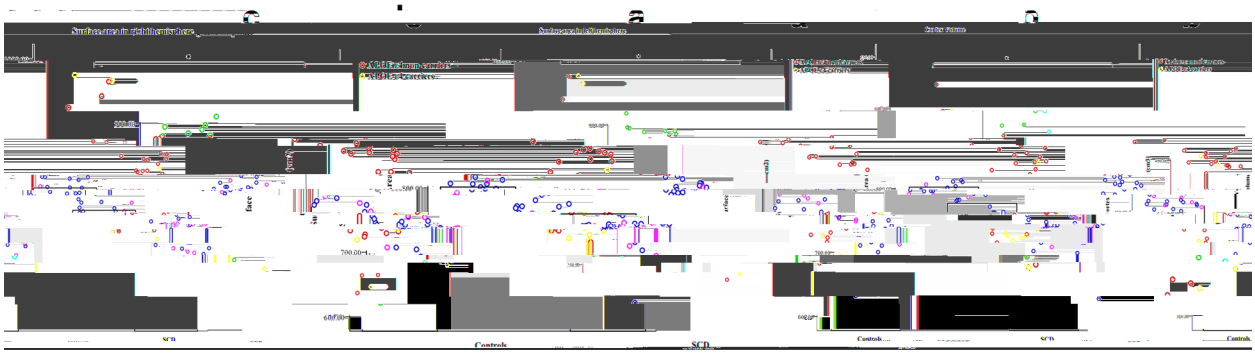

Fig. 1a – c Group differences in the cortex volume and bilateral surface area with a distribution of surface features in *APOE* ε4 carriers and non-carriers

that neuropsychiatric problems may act as an early risk

heritable, they were related to distinct genetic influences. The genetic influence on the surface area was explored to a greater degree, and early growth and development of the brain was found to be critical [59, 60]. The results of our study suggest that the cortical surface area rather than other metrics is influenced by genetic and emotional factors simultaneously, indicating that the surface area may be a more sensitive indicator for predicting AD. On the other hand, the discrepancy may be due to the differences in research standards and long continuous progress durations for individuals with SCD.

The present study presents some limitations and sheds an important light on the direction of future research. First, this is a cross-sectional data. The on-going multicenter longitudinal study, SILCODE, plays an important role in verifying the current assumptions and aims to establish a comprehensive estimation model for early detection as well as prediction in SCD. Second, with respect to interpretation of the correlation between the HAMA score and surface area in SCD ε4 carriers, the limited sample size should be taken into consideration. Third, in this study, we only used a HAMA single test to evaluate the anxiety symptoms for subjects with SCD. It would be important to include wider psychological tests to capture the neuropsychiatric performance in a more comprehensive manner.

Conclusions

The current study focuses on the ability of cortical morphology in SCD individuals to interact with *APOE* genotype and anxiety thereby predicting cognitive decline, and hopes to improve the understanding of heterogeneity in SCD and enrich clinical trials on SCD. In conclusion, certain genetic and affective problems, namely *APOE* ε4 and subclinical anxiety symptoms, were identified as risk factors of early-stage AD and may modulate brain structural marker expressions in SCD.

Additional file

Additional file 1: **Text S1.** Between-group comparisons of morphometric features in typical AD-related cortical regions. **Tables S1-S7.** Comparisons of bilateral surface area and cortical thickness in temporal lobe, parietal lobe, frontal lobe, occipital lobe, insula, cingulate and parahippocampal gyrus, separately, in SCD and controls. **Text S2.** Between-group comparisons of morphometric features in regions within default mode network (DMN). **Tables S8-S12.** Comparisons of surface area and cortical thickness value in bilateral parietal regions, bilateral posterior cingulated cortex (PCC), prefrontal cortex (PFC), bilateral temporal regions, and parahippocampal cortex within DMN, separately, in SCD and controls. (DOCX 331 kb)

Abbreviations

AD: Alzheimer's disease; *APOE*: Apolipoprotein E; AVLT-DR: Auditory Verbal Learning Test-delayed recall; AVLT-IR: Auditory Verbal Learning Test-immediate recall; AVLT-R: Auditory Verbal Learning Test-recognition; BNT: Boston Naming Test; CDR: Clinical Dementia Rating; FAQ: Functional Activities Questionnaire; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA-B: Montreal Cognitive Assessment Basic Version; SCD: Subjective cognitive decline; SILCODE: Sino-Longitudinal Cognitive Impairment and Dementia Study

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Authors' contributions

YS, XW, and YW did the manuscript preparation and drafting. YS, XW, YH, and JL did the clinical assessments and data acquisition. JL and YH did the clinical diagnosis. YS, YW, HD, TS, ME, FJ, and XNZ did the data analysis and interpretation. YH is responsible for the study conception and design. YS, XW, and YW contributed equally to this work. All authors have contributed to the manuscript revising and editing critically for important intellectual content and given final approval of the version and agreed to be accountable for all aspects of the work presented here.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the local ethics committee, and all individuals gave written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China. [2]CAS Key Laboratory of Behavioral Science and Research Center for Lifespan Development of Mind and Brain (CLIMB), Institute of Psychology, Beijing, China. [3]Department of Radiology, Xuanwu Hospital of Capital Medical University, Beijing, China. [4]Center for the Developing Brain, Child Mind Institute, New York, USA. [5]Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians-Universität (LMU), Munich, Germany. [6]Department of Psychiatry, Medical Faculty, University of Cologne, Cologne, Germany. [7]National Clinical Research Center for Geriatric Disorders, Beijing, China. [8]Beijing Institute of Geriatrics, Beijing, China. [9]Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China.

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