

Beneficial impact of education on cognition in amyloid-positive individuals with subjective cognitive decline: The SILCODE study

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Research

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Abstract

Background: Previous studies suggest that education is associated with a decreased risk of dementia in individuals with subjective cognitive decline (SCD). However, the influence of education on cognition in amyloid-positive SCD subjects is not clear.

Methods: We performed a cross-sectional study that involved 43 amyloid-negative and 29 amyloid-positive SCD subjects from the Sino Longitudinal Study on Cognitive Decline (SILCODE) project. Cognitive assessment included episodic memory, executive function, language, and general cognitive function. Multiple linear regression model was used to assess the association of education on cognitive performance.

Results: Multiple linear regression analysis suggested that education has a protective effect on executive function, language for the amyloid-negative SCD group and language, global cognition for the amyloid-positive SCD group.

Conclusions: The present study indicated that education has the potential to delay disease progression in amyloid-positive SCD subjects.

Introduction

Alzheimer's disease (AD) is the major cause of dementia in the elderly and its pathological hallmarks are the accumulation of β -amyloid (A β) plaques and neurofibrillary tangles [1]. Patients with AD typically present with memory loss and difficulties with thinking or language and that eventually leads to impairment for daily activities [2]. According to the latest data from the Global Burden of Diseases, Injuries, and Risk Factors Study, 43.8 million people suffer from dementia worldwide in 2016 [3]. For now, there is no approved disease-modifying treatments since 2003 though several medications can relieve the symptom [4]. Therefore, AD is a global public health priority. Nevertheless, accumulating evidence has proposed that people may have the potential to reduce their risk of cognitive decline, and dementia at an individual level [5]. Existing research reports that up to half of AD cases worldwide might be attributed to potentially modifiable risk factors and may be preventable through addressing these factors [6]. Education has been considered as one of the modifiable factor for AD. It was estimated that low educational attainment has the highest population-attributable risk (PAR) of AD worldwide (19.1%, 95% CI 12.3–25.6) [7]. Conversely, higher level of education has been shown to prevent or delay the onset of dementia [8,9].

Subjective cognitive decline (SCD) refers to a condition that an individual subjectively experienced decline in cognitive function in the absence of evidence for objective cognitive impairment [10]. Mounting evidence suggests that SCD is an early indicator of AD, which subjects with SCD are at high-risk for developing AD [11-13]. At the same time, it should be noted that the majority of individuals with SCD will not progress to AD [14]. In order to increase the likelihood of preclinical AD in individuals with SCD, a set of features (SCD-plus) was proposed in 2014 [10]. A β is a feature of the SCD-plus and A β positive (A β +)

SCD subjects is now considered the earliest symptomatic manifestation of Alzheimer's continuum (stage 2) [15]. Indeed, a recent study demonstrated that A β + SCD subjects were at increased risk of dementia, and showed a steeper decline on multiple cognitive domains including memory, attention, language, and executive functions compared to A β negative (A β -) individuals [16]. Therefore, A β + SCD population should be deserved greater attention in terms of prevention efforts. Our recent study found that education has the potential to delay or slow cognitive decline in individuals with SCD without the consideration of A β status [17]. Therefore, it is not clear whether education has a beneficial effect on cognition in A β + SCD subjects.

Here, we used data from the Sino Longitudinal Study on Cognitive Decline (SILCODE) project to explore the effect of education on memory, executive, language, and general cognitive functions in A β + SCD subjects. Our hypothesis was that education has a protective effect on cognition in A β + SCD individuals.

Methods

Study population

The data used in the present study were obtained from the SILCODE. SILCODE is a longitudinal study performed at Xuanwu Hospital of Capital Medical University, Beijing, China in April 2017, which aimed at identifying biomarkers related to the early diagnosis of AD by collecting multimodal neuroimaging data from the SCD population. This study was registered at ClinicalTrials.gov (number NCT03370744). And a detailed study protocol has been described elsewhere [18,19]. In summary, subjects participating in the SILCODE were asked to complete a series of clinical evaluation including medical history, physical and neurological examinations, neuropsychological tests, laboratory tests, and brain magnetic resonance imaging (MRI) scanning and as well as optional [^{18}F] florbetapir (AV-45) positron emission tomography (A β -PET) or [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) separately by a GE Signa integrated PET/MRI system (Germany) at baseline. The same examinations will be performed except for PET scans during the 15-month follow-up.

All eligible participants aged between 60 and 80 years old were Mandarin-speaking, had at least 6 years of education, and were right-handed. The individuals meeting the following conditions could be diagnosed as SCD: (1) with self-reported memory complaints; (2) failure to meet criteria for mild cognitive decline (MCI) [20], dementia due to AD established by the National Institute on Aging Alzheimer's Association workgroups (NIA-AA) [21], and any other disorders or condition that may cause cognitive impairment, such as stroke, traumatic brain injury or gas poisoning.

A total of 72 SCD subjects with A β -PET data available were selected for this study. With the use of pre-established cutoff value of 1.18 applied to the global AV45-PET standardized uptake value ratio (SUVR) [22], participants were subdivided into two groups: A β - SCD subjects ($\text{SUVR} \leq 1.18$, n=43) and A β + SCD subjects ($\text{SUVR} > 1.18$, n=29). For details see figure 1 for a flowchart.

Clinical and neuropsychological assessments

A paper case report form (CRF) was used to record demographic features (for example, name, age, gender, education, occupation, etc.), medical history, biochemical examination, a battery of neuropsychological tests and clinical diagnosis at the baseline and at different visits. In this study, we focus on 4 cognitive domains: episodic memory (Auditory Verbal Learning Test-Huashan version long-delayed free recall [AVLT-H-N5] and recognition [AVLT-H-N7]) [23], language (Animal Fluency Test [AFT]; Boston Naming Test [BNT]) [24,25], speed/executive function (Shape Trailing Test A [STT-A] and B [STT-B]) [26], global cognition (Montreal Cognitive Assessment-Basic [MoCA-B]) [27]. Details on neuropsychological tests published previously [19].

APOE genotyping

For each participant, a fasting blood sample was drawn in the department of laboratory, Xuanwu Hospital at baseline. A part of this blood sample was used for analysis of the level of blood glucose, blood lipids, anti-syphilis, homocysteine, folic acid, vitamin B12, thyroid hormone, hemoglobin, blood coagulation and the other part was used to determine the Apolipoprotein E (*ApoE*) gene polymorphism status. Details of *APOE* genotyping have been published elsewhere [19]. In this study, *APOE* genotype was dichotomized into SCD individuals with 1 or 2 copies of the *ε4 allele* (*APOE ε4* carriers) and those without any copies of the *ε4 allele* (*APOE ε4* non-carriers).

AV45-PET Analysis

PET images were preprocessed with statistical parametric mapping (SPM12, available at <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) software in MATLAB (version R2014a; MathWorks, Natick, MA, United States). For subjects with T1 scans, their PET images were registered to the corresponding structural MRI image. The structural MRI images were segmented into gray matter, white matter and cerebrospinal fluid tissue probability maps, in which nonlinear transformation parameters were obtained. Then, the non-linear transformation parameters were used to normalize the registered PET images into the Montreal Neurological Institute (MNI) stereotactic template. For subjects without T1 scans, their PET images were spatially normalized into MNI brain space with the TPM atlas. Then all PET images were resampled into $3 \times 3 \times 3 \text{ mm}^3$ voxels. Finally, normalized PET images were smoothed by an isotropic Gaussian smoothing kernel with the full-width at half maximum (FWHM) of $8 \times 8 \times 8 \text{ mm}^3$ to improve the signal-to-noise ratio. PET images were subsequently scaled to the whole cerebellum to get the SUVR maps. Then, mean SUVR maps of each group were obtained for visualization by MRICroN (available at <https://www.nitrc.org/projects/mricron>) to show the difference in A β level between the two groups.

Statistical analyses

First, continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables were reported as the mean \pm standard deviation, while not normally distributed variables were described as median \pm interquartile range. Categorical variables were expressed in absolute numbers and percentiles. Statistical differences between the two groups were analysed using *t* test, *Mann Whitney U*

test or *Chi-square* test. Second, explorative analysis probed the association between education and score of neuropsychological tests including AVLT-H-N5, AVLT-H-N7, STT-A, STT-B, AFT, BNT and MoCA-B. Third, multiple linear regression analysis was used to quantify the influence of education on cognitive function with the score of neuropsychological tests as the dependent variable and education as independent variables. Age, education, gender were entered as independent variables. Regression diagnostics were performed to ensure the assumptions for linear regression were met. Residuals were normally distributed. *Durbin-Watson* test statistics indicated independence of observations and heteroscedasticity was in conformance with test assumptions (results not shown). All statistical analyses were performed in R (R version 3.6.3). The significant level was set at $p < 0.05$ (2-sided).

Results

Subject characteristics

Demographic and clinical characteristics of the total sample and according to A β load are summarized in table 1. Of the 72 SCD participants, 43 (59.7%) were A β - and 29 (40.3%) were A β +. The average age was 65 years. The sample consisted predominantly of women (66.7%). The mean years of education was 12. The mean cortical SUVR of A β -PET values was 1.16. The proportion of *APOE* ϵ 4 carriers was 30.6%. There was no statistically significant difference between two groups in demographic characteristics and neuropsychological test scores. However, the SUVR of A β + SCD group was significantly higher than that of A β - SCD group. The SUVR maps of A β load were illustrated in figure 2 for each group. In addition, no subjects in the A β + SCD group had diabetes.

Effects of education on neuropsychological test scores

Correlation analysis revealed a significant correlation between education and STT-B ($r = -0.40, p < 0.01$), AFT ($r = 0.38, p < 0.05$), BNT ($r = 0.39, p < 0.01$), MoCA-B ($r = 0.38, p < 0.05$) in the A β - SCD group. And there was significant association between education and BNT ($r = 0.40, p < 0.05$) in the A β + SCD group.

Multiple linear regression analysis showed positive effects of education on STT-A ($\beta = -1.68, p = 0.046$), STT-B ($\beta = -4, p = 0.002$), AFT ($\beta = 0.68, p = 0.005$), BNT ($\beta = 0.27, p = 0.045$) for the A β - SCD group and BNT ($\beta = 0.42, p = 0.018$), MoCA-B ($\beta = 0.31, p = 0.019$) for the A β + SCD group (Figure 3).

Discussion

In the present study, we investigated the effects of education on multiple cognitive functions in A β + SCD subjects. The main finding of our study is that education has a beneficial effect on cognition in A β + SCD subjects.

Our recent study has shown that education exerted a protective effect on all neuropsychological tests among SCD subjects without explicit consideration of the A β status [17]. Thus, this study extends our previous findings and provides direct confirmation that education could have a positive influence on

cognitive function in A β + SCD individuals. Similarly to our results, a previous study demonstrated that education has a positive effect on attention, executive functioning, and global cognition in predementia participants (A β + SCD/MCI) [28]. Recently, a systematic review and meta analysis based on 243 observational prospective studies and 153 randomised controlled trials including a total of 44 676 studies proposed that people should receive as much education as possible in early life for AD prevention (*Class I, level A4*) [29]. It is generally believed that years of education could be considered a proxy used to measure cognitive reserve (CR) [30]. The concept of CR refers to the ability to use alternate functional brain processes to cope with brain pathology or cognitive aging to sustain normal performance levels on cognitive function [31]. The theory of CR contributed to explain the disparity between an individual's level of AD pathology and the clinical manifestation of those brain damages [32,33]. According to the theory, individuals with high CR remain clinically normal in the early stage of AD, but the rate of decline in cognitive performance is more rapid than in those with low CR in the late stage of AD [34]. Indeed, there is a considerable amount of evidence supports that higher levels of CR protect against progression of from SCD to MCI [35,36], and diagnostic conversion for normal cognition [37,38]. In this sense, our findings from this study are consistent with the theory of CR. However, the mechanism underlying the positive influence of education on cognitive function in A β + SCD subjects is not clear.

limitation

Strength of this study was that we use biomarker to increase the likelihood of SCD due to AD. However, this study has several limitations. First, this study was the cross-sectional design, and future studies evaluating the impact of education on progression for A β + SCD individuals longitudinally are desirable. Second, the sample size was small with only 72 subjects due to insufficient access to the opportunities of A β -PET scans, which may have affected the stability and accuracy of these results. Third, we used SUVR of A β levels of 1.18 to define A β positive status, as referred from the Alzheimer's Disease Neuroimaging Initiative. However, this cutoff value, developed in western countries, has not been validated in a Chinese population. Therefore, direct application of that cutoff value may lead to misclassification of our Chinese samples.

Conclusions

In summary, the present study found that education has the potential to delay disease progression for A β + SCD subjects. Therefore, improving the popularization of basic education may be a potentially promising approaches to preventing AD.

Abbreviations

AD: Alzheimer's disease, A β : β -amyloid, A β -PET: [^{18}F] florbetapir (AV-45) positron emission tomography, ApoE: Apolipoprotein E, AFT: Verbal Fluency Test, AVLT-H-N5: Auditory Verbal Learning Test-Huashan version long-delayed free recall, AVLT-H-N7: Auditory Verbal Learning Test-Huashan version long-delayed free recognition, BNT: Boston Naming Test, CRF: case report form, FDG-PET: [^{18}F] fluorodeoxyglucose

(FDG) positron emission tomography, HAMA: Hamilton Anxiety Scale, HAMD: Hamilton Depression Rating Scale, MCI: mild cognitive impairment, MNI: Montreal Neurological Institute, MoCA-B: Montreal Cognitive Assessment-Basic, MRI: magnetic resonance imaging, NC: normal control, NIA-AA: National Institute on Aging-Alzheimer's Association workgroups, SCD: Subjective cognitive decline, SILCODE: the Sino Longitudinal Study on Cognitive Decline. STT-A: Shape Trail Test A, STT-B: Shape Trail Test B. SUVR: standardized uptake value ratio.

Declarations

Ethics approval and consent to participate

The protocol of the study was approved by the medical ethics committee of Xuanwu Hospital of Capital Medical University, Beijing, China, and all participants gave their written informed consent before any study procedures began.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GC collected, analyzed, interpreted the data and drafted this manuscript. CL analyzed the data. KY revised this manuscript. XJ and YH designed this study and revised this manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Demographic and clinical characteristics of the study participants

	Total SCD (n=72)	A β - SCD (n=43)	A β + SCD (n=29)	<i>p</i>
Age, years	65(63,70)	66(63.5,69)	65(63,72)	0.804 [†]
Female, n (%)	48 (66.7)	26(60.5)	22(75.9)	0.269 [‡]
Education, years	12(11,15)	12(11,14.5)	12(12,16)	0.337 [†]
A β load (SUVR)	1.16 (1.09,1.21)	1.10 (1.04,1.14)	1.22 (1.20,1.26)	<0.001 [†]
HAMD	2.5(1,4.3)	2(1,4)	3(1,5)	0.36 [†]
HAMA	3(2,6)	3(2,6)	4(2,6)	0.804 [†]
AVLT-N5	7.6(2.0)	7.8(2.1)	7.3(1.8)	0.379 [§]
AVLT-N7	22(22,24)	22(21.5,24)	22(22,23)	0.758 [†]
STT-A	56.5(17.5)	57(14.9)	55.8(21.0)	0.774 [§]
STT-B	132.8(33.5)	128.8(26.6)	138.6(41.4)	0.226 [§]
AFT	19.7(4.6)	19.3(4.3)	20.3(4.9)	0.361 [§]
BNT	26(24,3)	25(24,28)	26(25,27)	0.963 [§]
MoCA-B	26.2(2.1)	26.2(2.0)	26.3(2.2)	0.802 [§]
Hypertension, n (%)	31(43.1)	20(46.5)	11(38.0)	0.632 [‡]
Diabetes, n (%)	8(11.1)	8(18.6)	0(0.0)	0.037 [‡]
Dyslipidemia, n (%)	28(38.9)	16(37.2)	12(41.4)	0.913 [‡]
<i>APOE</i> $\varepsilon 4$ status, n (%)	22(30.6)	13(30.2)	9(31.0)	1 [‡]

SCD subjective cognitive decline, *A β* β -amyloid, *A β -* A β negative, *A β +* A β positive, *SUVR* standardized uptake value ratio, *HAMD* Hamilton Depression Rating Scale, *HAMA* Hamilton Anxiety Scale, *AVLT-H-N5* Auditory Verbal Learning Test-Huashan Version for long-delayed free recall, *AVLT-H-N7* Auditory Verbal Learning Test-Huashan version long-delayed free recognition, *STT-A* Shape Trail Test A, *STT-B* Shape Trail Test B, *AFT* Verbal Fluency Test (animal), *BNT*Boston Naming Test, *MoCA-B* Montreal Cognitive Assessment-Basic. *APOE* $\varepsilon 4$ apolipoprotein $\varepsilon 4$.

[†]The p value was calculated using *Mann-Whitney U* test.

[‡]The p value was calculated using *Chi-square* test.

[§]The p value was calculated using independent samples *t* tests.

Figures

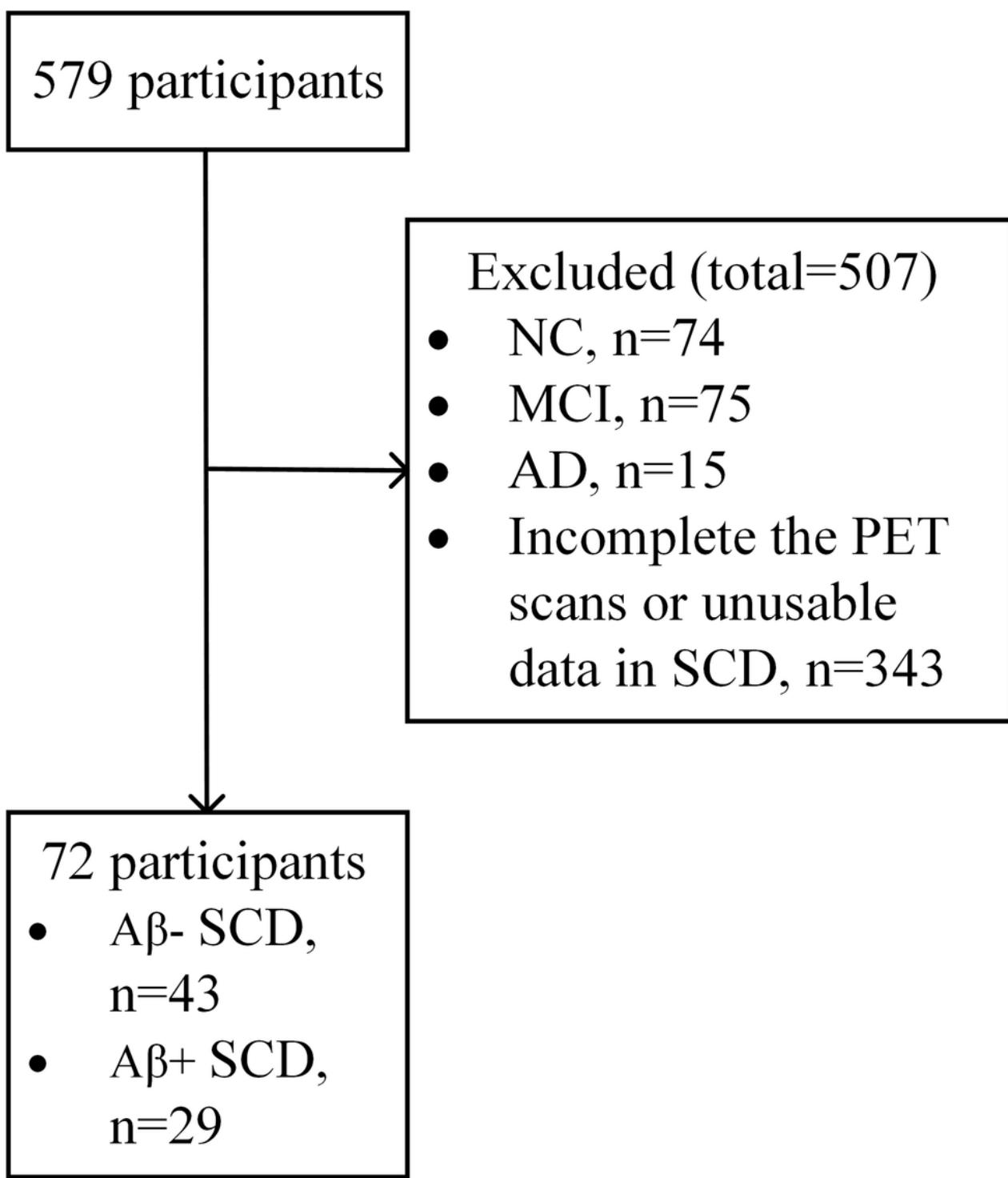


Figure 1

The flow chart of this study. NC normal control, MCI mild cognitive decline, AD Alzheimer's disease, PET positron emission tomography, SCD subjective cognitive decline, A β - A β negative, A β + A β positive.

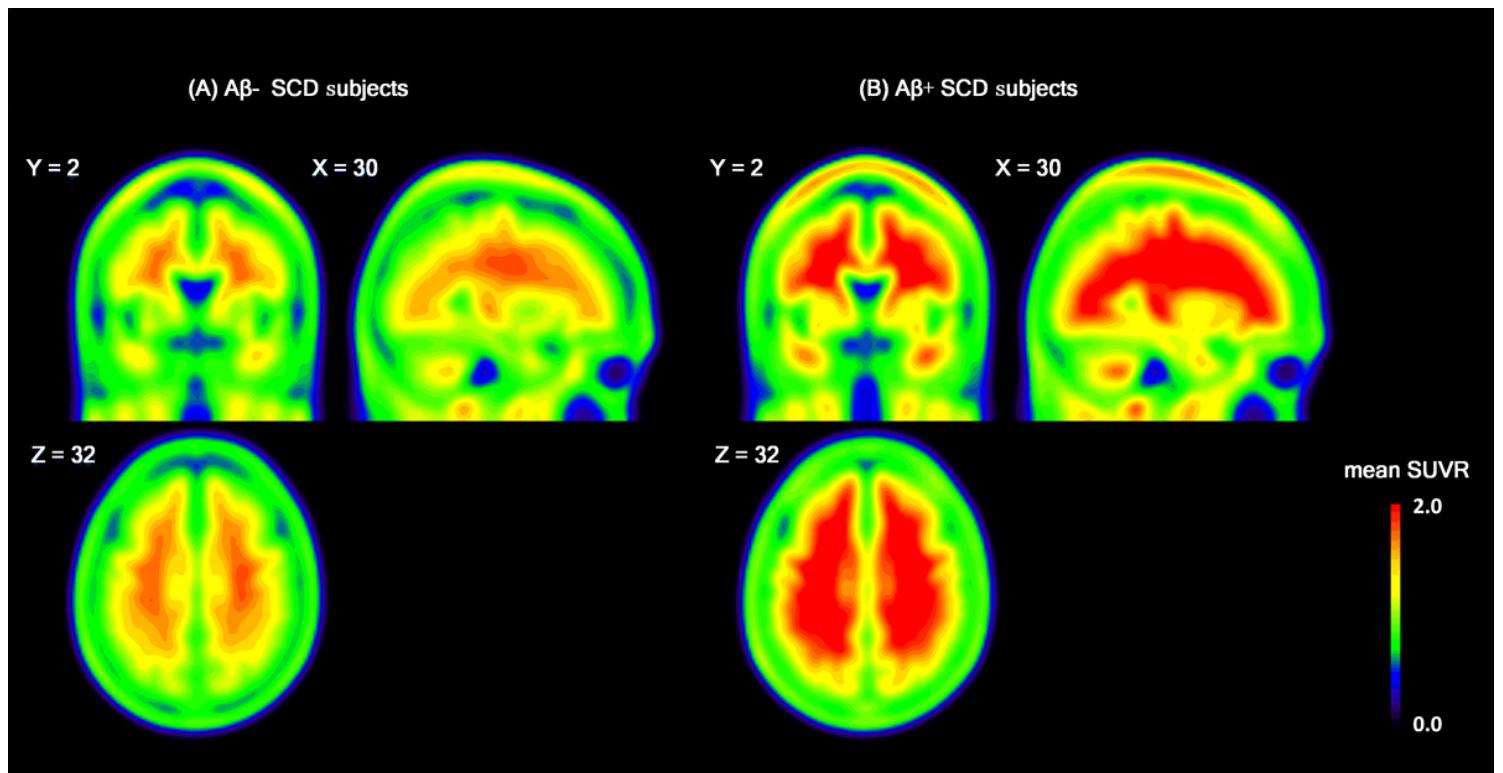


Figure 2

Comparison of SUVR in the two SCD groups. (A) Mean SUVR maps of A_β- SCD subjects, (B) Mean SUVR maps of A_β+ SCD subjects. The high end of the color scale (i.e., red) indicates relatively higher A_β deposition, whereas the low end of the scale (i.e., blue) represents lower A_β deposition.

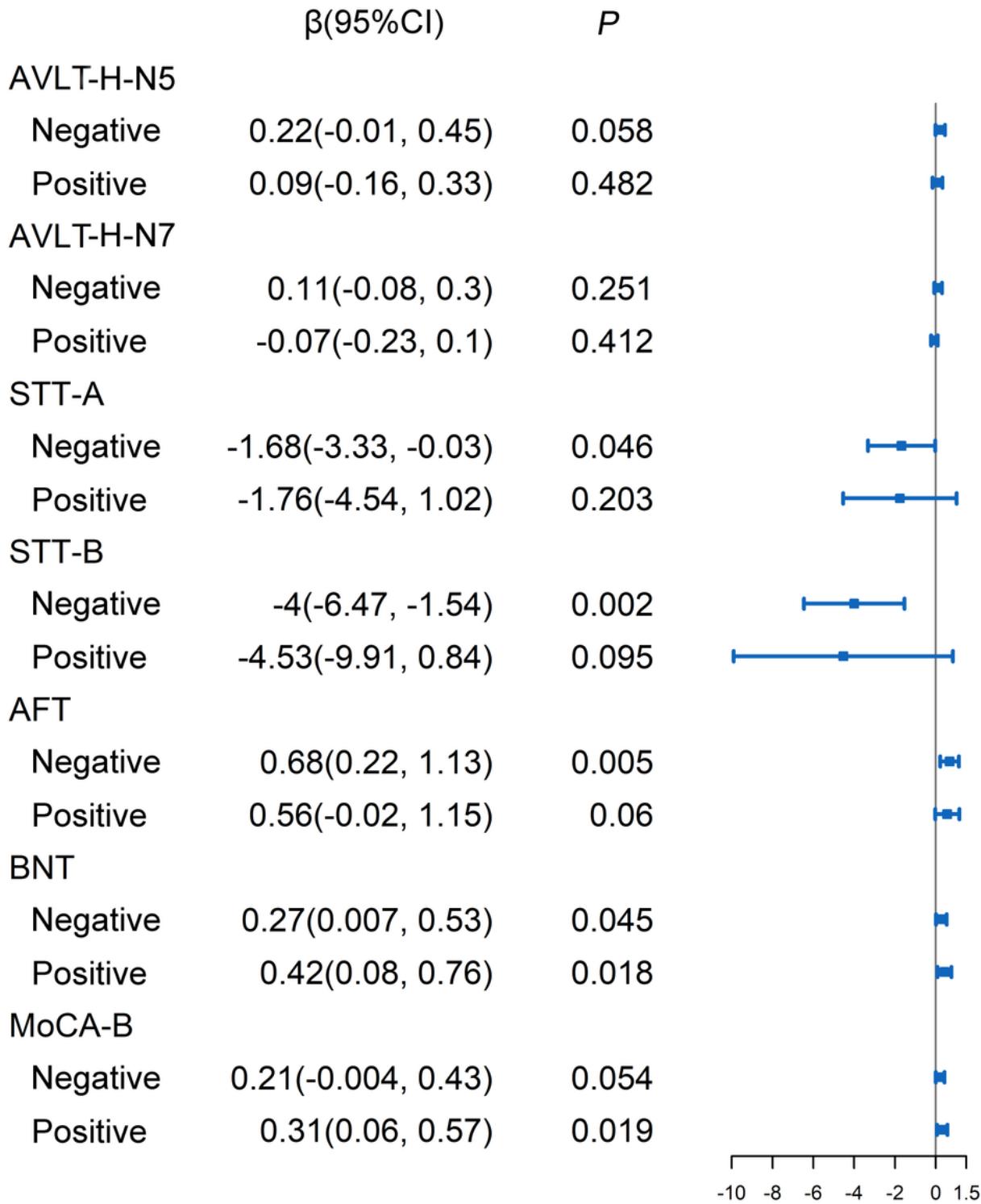


Figure 3

Effect sizes of education on cognitive measures in both A β - and A β + SCD subjects. β partial regression coefficients, CI confidence interval, AVLT-H-N5 Auditory Verbal Learning Test-Huashan Version for long-delayed free recall, AVLT-H-N7 Auditory Verbal Learning Test-Huashan version long-delayed free recognition, STT-A Shape Trail Test A, STT-B Shape Trail Test B, AFT Verbal Fluency Test (animal), BNT Boston Naming Test, MoCA-B Montreal Cognitive Assessment-Basic.