Neurobiology of Aging 138 (2024) 36–44

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Childhood engagement in cognitively stimulating activities moderates relationships between brain structure and cognitive function in adulthood

Alexandra M. Gaynor [a,b,c], Yunglin Gazes [a,b,d], Caleb R. Haynes [a,b], Reshma S. Babukutty [a,b], Christian Habeck [a,b,d], Yaakov Stern [a,b,d,e], Yian Gu [a,b,d,f,*]

[a] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, United States
[b] Cognitive Neuroscience Division, Department of Neurology, Columbia University, New York, NY, United States
[c] Montclair State University, Department of Psychology, Montclair, NJ, United States
[d] Gertrude H. Sergievsky Center, Columbia University, New York, NY, United States
[e] Department of Psychiatry, Columbia University, New York, NY, United States
[f] Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY, United States

ARTICLE INFO

Keywords:
Structural MRI
Cognitive performance
Aging
Cognitive reserve
Cognitive activities

ABSTRACT

Greater engagement in cognitively stimulating activities (CSA) during adulthood has been shown to protect against neurocognitive decline, but no studies have investigated whether CSA during childhood protects against effects of brain changes on cognition later in life. The current study tested the moderating role of childhood CSA in the relationships between brain structure and cognitive performance during adulthood. At baseline (N=250) and 5-year follow-up (N=204) healthy adults aged 20–80 underwent MRI to assess four structural brain measures and completed neuropsychological tests to measure three cognitive domains. Participants were categorized into low and high childhood CSA based on self-report questionnaires. Results of multivariable linear regressions analyzing interactions between CSA, brain structure, and cognition showed that higher childhood CSA was associated with a weaker relationship between cortical thickness and memory at baseline, and attenuated the effects of change in cortical thickness and brain volume on decline in processing speed over time. These findings suggest higher CSA during childhood may mitigate the effects of brain structure changes on cognitive function later in life.

1. Introduction

Past research has suggested greater levels of cognitive engagement have benefits for neurocognitive function across the lifespan. Greater educational attainment, for instance, has been associated with lower risk of neurodegenerative disease, as well as more intact brain structure, brain function, and cognitive function in both cross-sectional studies (Arenaza-Urquijo et al., 2013; Brickman et al., 2011; Chen et al., 2019; Cox et al., 2016; Foubert-Samier et al., 2012; Herrera et al., 2002; Le Carret et al., 2003; Mukadam et al., 2019; Stern et al., 1994; Teipel et al., 2010) and longitudinally over time (Chodosh et al., 2002; Christensen et al., 1997; Kramer et al., 2004; Montemurro et al., 2023; Valenzuela and Sachdev, 2006).

Furthermore, there is also a breadth of evidence suggesting education may significantly contribute to cognitive reserve, the ability to maintain cognitive function in the presence of age- or disease-related brain changes (Stern, 2009). For example, higher education has been associated with a weaker relationship between brain pathology and cognitive function (Bennett et al., 2005, 2003; Rentz et al., 2010), and when controlling for measures of clinical severity, higher education is associated with greater deficits in cerebral blood flow in patients with probable AD, suggesting education protects against clinical manifestations of neuropathological damage (Stern et al., 1992). The mechanisms underlying the contribution of educational attainment to cognitive reserve are thought to be related to engagement in cognitively stimulating activities, which may increase synaptic density and plasticity, and promote neurogenesis that protects against and/or compensates for age-related changes in brain structure and function (Baldivia et al., 2008; Sale et al., 2014). Although education is among the most commonly studied proxies of cognitive reserve, several studies have suggested educational attainment is limited in its use as a measure of cognitive reserve, given the influence of socioeconomic and cultural

* Correspondence to: Columbia University Medical Center, 622 W 168th St., P&H 18th floor, New York, NY 10032, Unites States.
E-mail address: yg2121@cumc.columbia.edu (Y. Gu).

https://doi.org/10.1016/j.neurobiolaging.2024.02.010
Received 30 June 2023; Received in revised form 16 February 2024; Accepted 21 February 2024
Available online 23 February 2024

factors in acquisition of formal education (Manly et al., 2003), and evidence that the protective role of education in cognitive reserve may be less consistent in highly educated samples, whereas early childhood education may confer greater benefits for later neurocognitive function (Christensen et al., 2006; Raz et al., 2010). Furthermore, cognitive function is significantly impacted by childhood cognitive experiences outside of formal education, including parental education (Kaplan et al., 2001; Rogers et al., 2009) and childhood stimulating cognitive milieu (Everson-Rose et al., 2003), indicating an important role for non-academic childhood cognitive engagement in neurocognitive function during adulthood.

Given evidence that the role of education in neurocognitive function may be driven by greater early engagement in cognitive activity, and the limitations of using education as a proxy for cognitive reserve, a measure of childhood cognitively stimulating activities (CSA) may serve as an alternative reflection of reserve acquired during early life. Cognitively stimulating environments have been shown to increase neurogenesis and factors related to neuroplasticity, which strengthen resilience against age- and disease-related pathological brain changes (Brown et al., 2003; Stern, 2009; Valenzuela and Sachdev, 2009). Several studies have provided evidence that greater levels of CSA during adulthood, such as reading books and newspapers, playing games and puzzles, or visiting museums, are associated with better cognitive performance across multiple domains (Wilson et al., 2003), as well as significantly reduced risk of Alzheimer's disease, dementia, and mild cognitive impairment, and lesser decline in cognitive function over time (Wilson et al., 2007, 2002b, 2002a). Research has also shown that CSA during adulthood contributes to cognitive reserve over and above the effects of formal education: controlling for clinical severity and formal education, individuals who engage in more cognitive activities have a greater degree of cerebral blood flow deficits, suggesting cognitive stimulation protects against the negative effects of brain pathology (Scarmeas et al., 2003).

Although there is significant evidence suggesting adult engagement in CSA is beneficial for neural and cognitive performance and may protect against age- or disease-related decline, few have tested whether greater CSA engagement during childhood contributes to cognitive reserve that is protective later in life. Given that early childhood education is thought to build brain and cognitive reserve, whereas more advanced levels of education appear to provide less significant benefits, it is possible that CSA during childhood may be a more appropriate measure, compared to adulthood CSA or childhood education that is inseparable from overall education, of the effects of early cognitive engagement on later-life neural and cognitive functioning.

The current study aimed to test whether CSA during childhood moderates the association between brain structure and cognitive performance cross-sectionally, and between longitudinal changes in brain structure and changes in cognitive performance over an average of 5 years in healthy adults. We hypothesized that greater engagement in childhood CSA would attenuate the relationship between brain structure and cognitive function, reflecting a protective role of CSA against neurocognitive decline.

2. Methods

2.1. Participants

The present study included adults aged 20–80 years, who completed both baseline and 5-year follow-up visits for two ongoing studies: the Reference Ability Neural Network (RANN) study (Stern et al., 2014) and the Cognitive Reserve study (Stern et al., 2018), both conducted at Columbia University Irving Medical Center with similar recruitment and research procedures.

At baseline, 651 participants were enrolled across both studies. As of March 2023, 338 participants returned for a follow-up visit after an average of 5 years. For the current analyses, participants were excluded if they did not have Childhood Cognitively Stimulating Activities questionnaire data (N=65) or baseline structural MRI data (N=8); a further 14 participants were excluded for missing IQ data, resulting in a final sample size of N=250 at baseline. For longitudinal analyses, a further 41 participants were excluded for missing follow-up structural MRI data, and 5 for missing follow-up cognitive function data, resulting in a sample size of N=204 at follow-up.

All participants were native English speakers, right-handed, free of MRI contraindications, and read at a fourth-grade level or above. No participants had any psychological or medical conditions that could affect cognitive function, and no older adults met criteria for dementia or MCI. All participants provided informed consent, and all methods were approved by and performed in accordance with the relevant guidelines and regulations of the Institutional Review Board of the College of Physicians and Surgeons of Columbia University and with the ethical standards of the 1964 Declaration of Helsinki.

2.2. Cognitive function

Cognitive function was measured at both baseline and follow-up visits using performance on three neuropsychological tests for each of three reference abilities (RAs): memory (MEMORY), fluid reasoning (FLUID), and processing speed and attention (SPEED). MEMORY composite score was measured by the Selective Reminding Task subtests of long-term storage, continuous long-term retrieval, and words recalled on last trial (Buschke and Fuld, 1974). FLUID composite score was measured using WAISIII Block design, WAIS-III Letter–Number Sequencing, and WAISIII Matrix Reasoning test (Wechsler, 1997). SPEED score was estimated using WAIS-R Digit Symbol subtest (Wechsler, 1987), Trail Making test Part A (Reitan, 1971), and Stroop Color naming subtest (Golden et al., 2012). Performance on each task was z-scored relative to the mean and standard deviation in participants of the entire study sample. Z-scores for tests within each cognitive domain were then averaged to produce three reference ability z-scores for each participant. Longitudinal cognitive change scores were calculated as follow-up scores minus baseline scores.

2.3. Cognitively stimulating activities

Childhood cognitively stimulating activities (CSA) were measured using a validated self-report questionnaire (Wilson et al., 2003) in which participants rated on a 5-point scale the frequency with which they engaged in nine cognitive activities during childhood: every day or about every day (5 points), several times a week (4 points), several times a month (3 points), several times a year (2 points), and once a year or less (1 point). Participants reported how frequently they had each of the following 9 activities: were read to, played a game, or told stories at age 6, and visited a library, wrote a letter, played a game, or read a newspaper, magazine, or book at age 12. Responses were averaged to produce a composite mean Childhood CSA score, ranging from 1 to 5, with higher values indicating greater engagement in CSA. Childhood CSA scores were categorized into two groups (low; high) based on median of total scores. Analyses were conducted using CSA scores collected at follow-up, as the questionnaire was only administered to a small number of participants at baseline; however, for N=29 participants who had CSA data at both timepoints, there were no significant differences in mean childhood CSA scores.

2.4. MRI procedures

Magnetic resonance images were acquired on a 3.0 Tesla Philips Achieva Magnet, over two 2-h sessions. T1-weighted whole brain images were acquired for each participant using magnetization-prepared rapid gradient-echo (MPRAGE) sequence with TE/TR of 3/6.5 ms and Flip Angle of 8 degrees, in-plane resolution of 256×256, field of view 55.4×25.4 cm and 165–180 slices in axial direction with slice-thickness/

gap of 1/0 mm. Fluid Attenuated Inverse Recovery (FLAIR) images were collected with the following parameters: 11,000 ms repetition time, 2800 ms echo time, 256×189 voxels in-plane resolution, 23.0×17.96 cm field of view, and 30 slices with slice-thickness/gap of 4/0.5 mm) (Yendiki et al., 2011). FreeSurfer software (v.5.1) was used for reconstruction of T1 scans and for calculation of mean cortical thickness based on 68 cortical regions of interest (Desikan et al., 2006). Two diffusion MRI were acquired in 56 directions using the following parameters: b = 800 s/mm^2, TE = 69 ms, TR = 11,032 ms, flip angle = 90 degrees, in-plane resolution 112×112 voxels, acquisition time = 12 min 56 s, slice thickness = 2 mm (no gap), and 75 slices. Diffusion data were analyzed with version 3.0.1 of the software MRtrix3 (www.mrtrix.org), starting with a set of preprocessing steps to improve data robustness: (1) denoising (Veraart et al., 2016), (2) Gibbs ring correction (Kellner et al., 2016), (3) corrections for motion and eddy currents (FSL eddy) (Andersson and Sotiropoulos, 2016) and (4) bias field correction (Tustison et al., 2010). Diffusion tensor models were estimated for the preprocessed data from which fractional anisotropy (FA) was calculated for each participant. To calculate the mean FA for the white matter across the whole brain, each participant's T1 structural scan was registered to the mean of the non-diffusion weighted images, and then parcellated on FreeSurfer. The derived white matter mask was then used to quantify each participant's mean MD across all white matter in the brain, resulting in one MD value per participant and used in LCSM described below. White matter hyperintensity (WMH) was derived from FLAIR imaging (Yendiki et al., 2011). Using the Lesion Segmentation Toolbox for Statistical Parametric Mapping, images were visually inspected and manually corrected for errors, and WMH volumes were log transformed prior to analysis. Cortical thickness values are reported in units of millimeters (mm), total brain volume is reported in cubic centimeters (cm^3), white matter hyperintensity burden is reported in cubic millimeters (mm^3), and DTI FA values reflect a range from 0 to 1 with higher number representing more intact white matter integrity.

2.5. Data analyses

Descriptive statistics were used to present participant characteristics including age, education (number of years in school), sex, race, ethnicity, and IQ scores, and chi-squared tests and one-way analyses of variance were used to test differences between CSA groups. Multivariable linear regression models were used to examine the interaction between CSA group and brain structure on cognitive performance at baseline, and between CSA group and change in brain structure on change in cognitive performance over 5 years. Change scores were calculated as follow-up minus baseline values. All models were adjusted for age, sex, race, education, and NART IQ (Nelson, 1982). The following number of participants were excluded from relevant models due to extreme outlier longitudinal data based on Tukey's hinges (more than 1.5 x interquartile range beyond first and third quartiles): MEMORY: 1; FLUID: 1; SPEED: 3; cortical thickness: 2; WMH: 2; total brain volume: 1; FA: 9. All analyses were conducted in SPSS (version 28.0). Statistical significance was indicated by two-sided $p<.05$, with $p<.10$ considered trending toward significance.

3. Results

3.1. Descriptive analyses

At baseline, participants were on average 56.28 (SD=15.79, range 22–80, median=62) years old (Supplemental Fig S1), and had a mean of 16.16 (SD=2.21, range 12–20) years of education. About 57% were female, and 23.3%, 68.4%, and 8.4% identified as black/African American, white, and other race, respectively. Mean NART IQ score was 119.02 (SD= 7.92, range 90.32–129.76).

The total participant sample had a mean CSA score of 3.24 (SD= 0.66, range 1.33–4.78). The low CSA group had a mean CSA score of 2.81 (SD= 0.43, range 1.33–3.33) and the high CSA group had a mean score of 3.91 (SD=0.32, range 3.44–4.78). One-way analyses of variance showed there were no significant differences between CSA groups in baseline age, IQ, cognitive performance, mean cortical thickness, white matter hyperintensities, or FA. Education and baseline total brain volume were significantly higher for the high CSA group. There were no significant group differences in any longitudinal measures of change in performance or brain structure. Chi-squared tests showed CSA groups did not differ by race or sex (Table 1). Pearson's correlations showed that at baseline, all RAs (FLUID, MEMORY, SPEED) were significantly positively correlated with total brain volume, cortical thickness, and DTI FA, and significantly negatively correlated with mean WMH (Supplemental Table 3).

Over an average of 5 years from baseline to follow-up visits, mean cognitive performance decreased for MEMORY (M= −0.109, SD= 0.830), FLUID (M= −0.201, SD= 0.498), and SPEED (M= −0.246, SD= 0.528). Mean cortical thickness, total brain volume, and FA also decreased, with an average change of (M= −0.044, SD= 0.073), (M= −20.112, SD= 24.802), and (M= −0.019, SD= 0.053), respectively. Mean WMH increased from baseline to follow-up visits (M= 0.324, SD= 0.443).

3.2. Interaction between CSA and structural brain measures on cognitive performance at baseline

We found a significant interaction between CSA group and baseline cortical thickness on baseline MEMORY performance (B=−1.755 [−3.344, −0.166], p<.05), wherein the high CSA group showed a weaker positive association between thickness and performance (Table 2; Figure 1). There were no other significant interactions between

Table 1
Participant characteristics by childhood CSA group.

	Low CSA	High CSA	Sig. (p)
N BL	112	138	
Age BL (years)	56.57 (16.02)	56.05 (15.66)	.796
Education BL (years)	15.65 (2.20)	16.57 (2.14)	<.001***
% Female	58.0	55.8	.722
% White	62.5	73.2	.314[a]
% Black / African American	26.8	20.3	
% Other race	10.7	6.5	
NART IQ BL	118.80 (7.83)	119.19 (8.02)	.700
MEMORY BL	0.01 (0.94)	0.16 (0.84)	.194
FLUID BL	0.01 (0.88)	0.15 (0.76)	.177
SPEED BL	-0.07 (0.86)	0.08 (0.80)	.171
Cortical Thickness BL (mm)	2.54 (0.12)	2.54 (0.12)	.881
WMH BL (mm^3)	2.36 (0.95)	2.45 (0.96)	.510
Total Brain Volume BL (cm^3)	1059.52 (112.98)	1090.98 (107.18)	.025*
DTI FA BL	0.37 (0.03)	0.37 (0.03)	.427
N Longitudinal	87	117	
MEMORY Δ	0.01 (0.79)	-0.18 (0.83)	.111
FLUID Δ	-0.14 (0.45)	-0.19 (0.50)	.459
SPEED Δ	-0.24 (0.49)	-0.23 (0.51)	.810
Cortical Thickness Δ (mm)	-0.04 (0.06)	-0.05 (0.08)	.216
WMH Δ (mm^3)	0.26 (0.30)	0.38 (0.45)	.058
Total Brain Volume Δ (cm^3)	-18.88 (17.53)	-20.89 (29.31)	.571
DTI FA Δ	-0.01 (0.04)	-0.02 (0.05)	.319

***p<.001; *p<.05.
[a]p-value reflects chi-square test of all 3 race/ethnicity categories by OPA group. Mean (SD) reported for continuous outcomes, percentages reported for categorical outcomes.
p-values reflect differences between CSA groups based on one-way ANOVAs and Pearson's chi-square tests.
Abbreviations: BL= baseline; Δ = change from baseline to follow-up; WMH= white matter hyperintensities; DTI FA= fractional anisotropy; FLUID= fluid reasoning; MEMORY= episodic memory; SPEED= perceptual speed.
Note: Total sample sizes for several individual measures varied due to missing data as follows: WMH BL: 205; DTI FA BL: 228; WMH Δ: 148; DTI FA Δ: 139.

Table 2
Interaction between childhood CSA group and brain structure on performance for each reference ability at baseline.

	Cortical Thickness		DTI FA		Total Brain Volume		WMH	
	B [LL, UL]	*p*	B [LL, UL]	*p*	B [LL, UL]	*p*	B [LL, UL]	*p*
MEMORY	-1.76 [−3.34, −0.17]	.03*	-3.17 [−10.24, 3.90]	.38	-0.00 [−0.00, 0.00]	.10	-0.06 [−0.24, 0.17]	.63
FLUID	-1.18 [−2.54, 0.18]	.09†	-5.40 [−11.48, 0.68]	.08†	-0.00 [−0.00, 0.00]	.97	-0.03 [−0.22, 0.15]	.72
SPEED	-0.03 [−1.38, 1.31]	.96	-3.29 [−9.18, 2.73]	.29	0.00 [−0.00, 0.00]	.56	0.13 [−0.06, 0.32]	.17

*p<.05; †p<.10.
B= unstandardized regression coefficient, with 95% Wald confidence intervals [LL: lower limit, UL: upper limit].
Abbreviations: DTI FA= diffusion tensor imaging fractional anisotropy; WMH= white matter hyperintensities; MEMORY= episodic memory; FLUID= fluid reasoning; SPEED= perceptual speed.

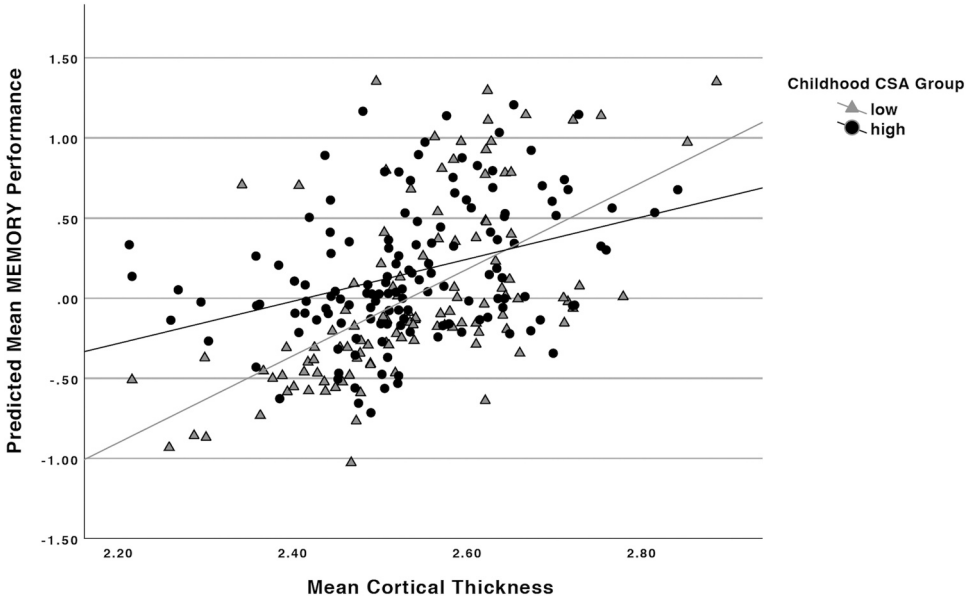

Fig. 1. Relationship between baseline mean cortical thickness and memory performance by childhood CSA group. Results of multivariable linear regressions modeling interaction between childhood CSA group and baseline mean cortical thickness on baseline memory performance. Models adjusted for effects of age, education, gender, race, and IQ.

CSA group and baseline structural measures on MEMORY. For FLUID, the interaction between CSA group and brain structure on performance was trending toward significance for cortical thickness (B=−1.180 [−2.543, 0.183] p=.09) and for FA (B=−5.404 [−11.483, 0.676], p=0.08), with a weaker effect of brain structure on FLUID performance for the high CSA group relative to low CSA. For SPEED, CSA group did not moderate the associations between any of the structural measures and cognitive performance (Table 2).

3.3. Interaction between CSA and change in brain structure on change in cognitive performance

There were no significant interactions between CSA group and change in any of the four structural measures on change in MEMORY or FLUID performance (Table 3). For SPEED, CSA group significantly moderated the effect of change in cortical thickness on change in performance (B=−3.31 [−5.20, 1.42], p<.001); those with low CSA showed greater decrease in SPEED performance with greater decrease in cortical thickness, but this effect was not seen in the high CSA group (Table 3; Figure 2). CSA group also significantly moderated the effect of change in total brain volume on change in SPEED (B=−0.01 [−0.02, −0.00], p<.01) with the higher CSA group showing an attenuated effect of decline in brain volume on decline in SPEED performance relative to low CSA (Table 3; Figure 3). The interaction between CSA group and FA on SPEED trended toward significance (B=3.31 [−0.19, 6.81], p=.06), wherein there was an overall positive relationship between FA change and SPEED change as expected, but here the low CSA group showed a weaker effect of change in structure on change in performance relative

Table 3
Interaction between childhood CSA group and longitudinal change in brain structure on change in performance for each reference ability.

	Cortical Thickness Δ		DTI FA Δ		Total Brain Volume Δ		WMH Δ	
	B [LL, UL]	*p*	B [LL, UL]	*p*	B [LL, UL]	*p*	B [LL, UL]	*p*
MEMORY Δ	-0.045 [−3.37, 3.28]	.98	-2.08 [−8.35, 4.19]	.52	0.01 [−0.00, 0.02]	.17	-0.57 [−1.27, 0.13]	.11
FLUID Δ	-0.48 [−2.46, 1.50]	.64	-0.62 [−4.43, 3.18]	.75	-0.00 [−0.01, 0.01]	.86	0.08 [−0.36, 0.51]	.73
SPEED Δ	-3.31 [−5.20, −1.42]	<.001***	3.31 [−0.21, 6.83]	.07†	-0.01 [−0.02, −0.00]	.01**	-0.08 [−0.49, 0.32]	.70

***p<.001; **p<.01; *p<.05; †p<.10.
B= unstandardized regression coefficient, with 95% Wald confidence intervals [LL: lower limit, UL: upper limit].
Abbreviations: Δ= change from baseline to follow-up; DTI FA= diffusion tensor imaging fractional anisotropy; WMH= white matter hyperintensities; MEMORY= episodic memory; FLUID= fluid reasoning; SPEED= perceptual speed.

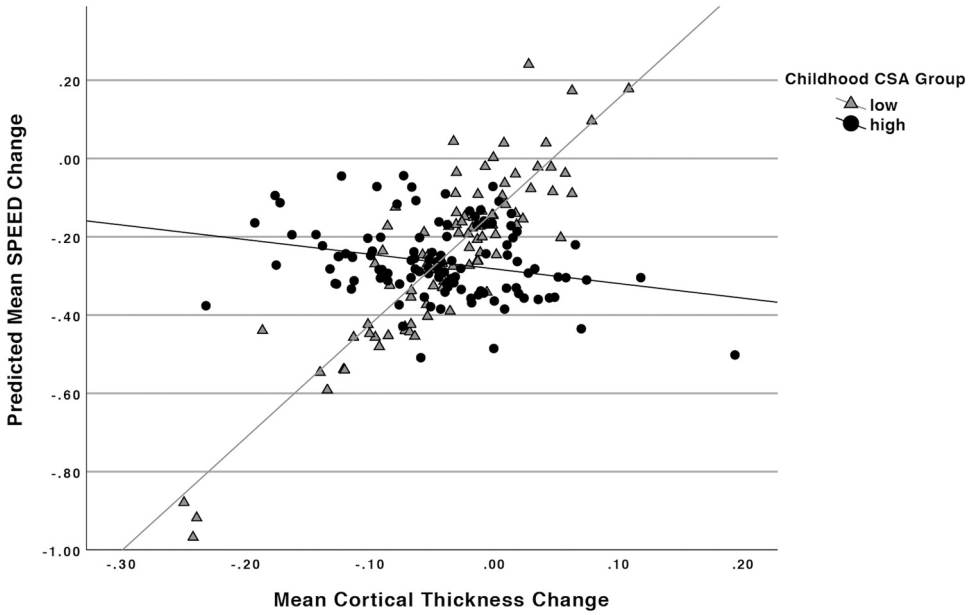

Fig. 2. Relationship between change in mean cortical thickness and change in processing speed performance by childhood CSA group. Results of multivariable linear regressions modeling interaction between childhood CSA group and change in mean cortical thickness on change in processing speed performance. Models adjusted for effects of age, education, gender, race, and IQ.

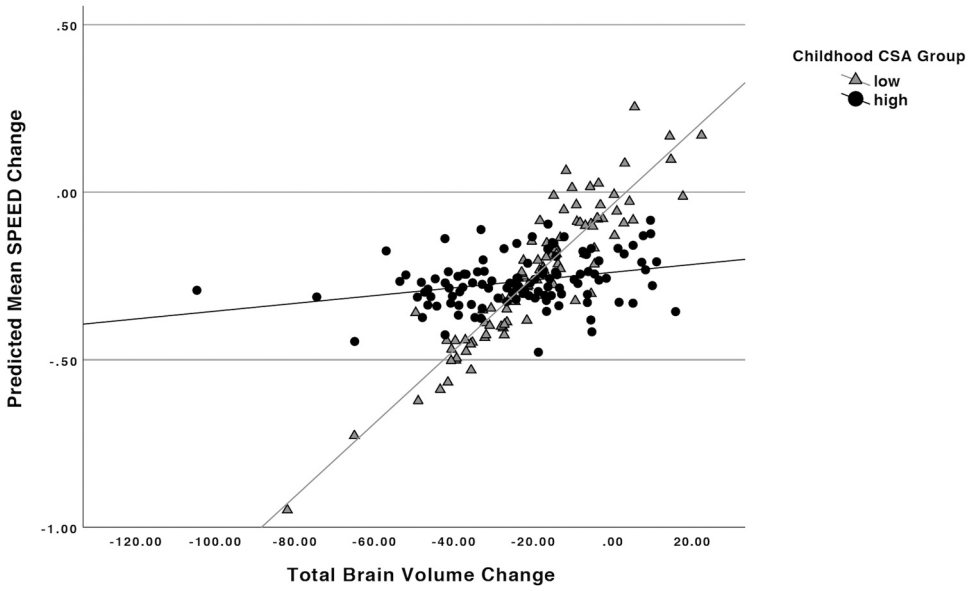

Fig. 3. Relationship between change in total brain volume and change in processing speed performance by childhood CSA group. Results of multivariable linear regressions modeling interaction between childhood CSA group and change in total brain volume on change in processing speed performance. Models adjusted for effects of age, education, gender, race, and IQ.

to the high CSA group.

3.4. Sensitivity analyses

Sensitivity analyses were conducted on significant interactions using continuous childhood CSA scores rather than categorized childhood CSA groups. Results showed that the moderating effect of childhood CSA on the relationship between baseline MEMORY and baseline cortical thickness was marginally significant (B=−1.21 [−2.43, 0.015], p=.053). For longitudinal change, the interaction between childhood CSA and changes in brain structure on changes in SPEED performance remained statistically significant for both cortical thickness (B=−2.66 [−4.22, −1.10], p<.001) and total brain volume (B=−0.01 [−0.01, −0.00], p<.01).

To determine whether significant interactions between childhood CSA and structural change on cognitive change were driven by specific age groups, sensitivity analyses were conducted on significant longitudinal interactions stratifying by age groups defined by tertiles. Results showed that the interaction between childhood CSA and cortical thickness change on SPEED change was marginally significant in the young group (B=−4.44 [−8.93, 0.05], p=.052), and significant in the middle age group (B=−3.78 [−6.77, −0.78], p<.05) and older group (B=−3.14 [−6.05, −0.22], p<.05). The interaction between childhood CSA and total brain volume change on SPEED change was significant in

the young age group (B=−0.03 [−0.04, −0.01], $p<.01$); effects in middle and older age groups did not reach statistical significance, but showed results trending in the same direction, wherein higher childhood CSA was associated with an attenuated effect of decline in brain volume on decline in SPEED, suggesting results were not driven by a specific age group. Descriptive statistics for change in structural measures by age group can be found in Supplemental Table 1.

4. Discussion

In the current longitudinal population-based study, we found that for adults aged 20–80, higher engagement in cognitively stimulating activities during childhood moderated the relationship between cortical thickness and episodic memory performance at baseline. In longitudinal analyses, higher childhood CSA also attenuated the effects of changes in cortical thickness and total brain volume on changes in speed performance over an average of 5 years. To our knowledge, this is the first study to test the relationship among childhood CSA, structural measures of brain health, and cognitive performance cross-sectionally and longitudinally, and demonstrate that childhood CSA may benefit cognition during adulthood by mitigating the negative effects of changes in brain structure on cognition.

We found evidence that childhood CSA moderated the positive association between cortical thickness and episodic memory at baseline, wherein individuals with higher childhood CSA showed similar memory performance irrespective of cortical thickness. This is consistent with other cross-sectional studies reporting that cognitive lifestyle measures are positively associated with cortical thickness in memory-related brain regions (Valenzuela et al., 2012), and that cognitive reserve, indicated by functional connectivity patterns, moderates relationships between cortical thickness and memory performance (Stern et al., 2021). Although moderation effects on other measures of brain structure and cognition did not reach statistical significance, there were marginally significant interactions consistently in the expected direction, i.e., those with high childhood CSA showed a weaker relationship between both cortical thickness and FA on fluid reasoning performance, suggesting the protective effect of higher childhood CSA may be consistent across multiple measures of brain structure and domains of cognitive function.

In analyses of longitudinal change in brain structure and cognitive abilities, childhood CSA had a significant moderating role in the effects of changes in mean cortical thickness and total brain volume on changes in processing speed performance but did not significantly moderate effects of change in structure on other cognitive abilities. This is consistent with past research reporting an effect of cognitive activity on perceptual speed but not memory (Wilson et al., 2003), evidence that the moderating role of education on the relationship between neuritic plaques and performance is strongest for perceptual speed relative to other domains (Bennett et al., 2005), and recent longitudinal work from our group showing education moderates the effect of changes in diffusivity and cortical thickness on processing speed but not memory or fluid reasoning (Gazes et al., 2023). Furthermore, these results highlight the differences in contributions of CSA as compared to education in CR, as studies on the latter have reported that education may be a less sensitive predictor of processing speed than other domains (Christensen et al., 1997). Although interaction analyses for other cognitive domains did not reach statistical significance in the current sample, childhood CSA showed a similar effect on memory and fluid reasoning, wherein the majority of associations between brain change and decline in cognitive performance were mitigated by higher childhood CSA levels. A breadth of research has shown that cortical thickness is negatively associated with age, (Ecker et al., 2009; Fjell and Walhovd, 2010; Salthouse et al., 2015) and that greater cortical thickness is associated with better cognitive function in multiple domains throughout the lifespan (Fjell and Walhovd, 2010; Karama et al., 2009; Salthouse et al., 2015; Westlye et al., 2011). Given that decreases in cortical thickness likely contribute to age-related declines in cognitive ability, the current study offers important insight into potential protective factors early in life that may attenuate the negative sequelae of decreasing structural integrity during adulthood.

It should be noted that we found a moderately significant interaction among childhood CSA group, FA change, and SPEED change, wherein the high CSA group showed a greater effect of FA change on decline in performance. We speculate that the unexpected direction of the moderating effect of CSA here may be due to relatively limited sample sizes in models evaluating FA change compared to our analyses of other structural measures. However, past research has shown differential effects of aging on grey matter and white matter, wherein cognitive complaints are more strongly associated with changes in cortical thickness than with white matter changes (Cedres et al., 2021), and there is evidence that white matter changes may precede grey matter changes in aging (Mooij et al., 2018). Therefore, it is possible that in individuals with lower childhood CSA, cognition is more reliant on gray matter health, whereas those with higher childhood CSA are still able to rely on white matter health. Further research using larger sample sizes is warranted to better elucidate the role of childhood CSA in the relationship between white matter integrity measures, grey matter changes, and cognitive performance.

Whereas the majority of existing research on the effects of cognitive stimulation on brain and cognitive function has focused on engagement in cognitive activities during adulthood, the present study is the first of our knowledge to provide evidence of the role of childhood cognitive activities in moderating the relationship between brain structure and cognition in adulthood. Importantly, we found that engaging in CSA during childhood had a protective effect over and above the role of education, a common proxy of cognitive reserve. However, similarly to educational attainment, differences in childhood CSA are likely impacted by sociocultural factors such as parental education and socioeconomic status (SES). As such, increasing engagement in CSA during childhood may be a target for reducing disparities in cognitive reserve, particularly in children with less access to high quality or advanced levels of formal education.

It is worth noting that in addition to childhood CSA, current engagement in CSA may also contribute to brain and cognitive changes across the lifespan. There is evidence that early life factors are critical to the development of cognitive reserve capacity (Chapko et al., 2018; Dekhtyar et al., 2015; Lesuis et al., 2018), whereas lifelong engagement in CSA is likely to contribute to brain maintenance (Barulli and Stern, 2013; Nyberg et al., 2012). Therefore, the current study evaluated the role of childhood CSA based on the hypothesis that its moderating role in the relationship between brain structure and cognition reflects cognitive reserve. Nevertheless, it is likely that childhood and adulthood CSA interact in their effects on neurocognitive function in adulthood, and there is evidence that the effects of childhood CSA on cognition in adults may be reduced when controlling for effects of current CSA (Wilson et al., 2005). In the current sample, interactions between childhood CSA and structural changes on change in cognitive performance remained significant even when controlling for effects of current CSA, suggesting childhood CSA may confer protection against cognitive sequelae of brain changes irrespective of current engagement in CSA.

The mechanisms by which high childhood CSA contributes to cognitive reserve remain unclear; however, past research has suggested lower levels of cognitive stimulation during childhood limit early learning, which may lead to excessive synaptic pruning during development. Children raised in environments lacking cognitive and social stimulation have also been shown to have reduced white matter integrity, which is correlated with increased neurocognitive deficits (Hanson et al., 2013; Rosen et al., 2018). Animal studies have further suggested that enriched and stimulating environments lead to molecular and anatomical changes that result in greater neuroplasticity (Hirase and Shinohara, 2014). It is possible that childhood CSA contributes to cognitive reserve by increasing capacity for neuroplasticity, which facilitates the recruitment of compensatory neural structures or networks to maintain cognition in the face of brain changes.(Barulli and Stern,

2013; Becker et al., 1996; Stern et al., 1999) Higher engagement in CSA may also provide cognitive strategies that allow individuals to perform normally on cognitive tasks despite brain pathology,(Barulli et al., 2013) and indeed studies have shown that older adults with higher SES employ more mnemonic strategies during memory tasks than lower-SES adults (Czernochowski et al., 2008). Therefore, early life CSA may contribute to reserve by promoting neural changes and/or strategic skills that maintain cognition in the face of age-related brain changes.

The current study is strengthened by the inclusion of adults across a broad age range, as well as adjusting for the potential confounding effects of education and IQ on cognitive reserve, demonstrating that early engagement in cognitively stimulating activities confers a protective effect against structural brain changes over and above the contributions of common proxies of cognitive reserve. This study is further strengthened by the use of a validated measure of childhood cognitively stimulating activities, which has been shown to predict performance in a breadth of cognitive domains, as well as measures of neuropathological burden and risk of dementia and Alzheimer's disease (Wilson et al., 2003, 2013, 2007, 2002b).

Despite these strengths, the current study is subject to several limitations. The participant sample was drawn from the New York City metropolitan area, and results may be less generalizable for populations with significantly different socioeconomic and cultural factors that impact childhood environments. Childhood SES in particular has been shown to impact cognitive function in adulthood,(Kaplan et al., 2001) and there is evidence that higher family SES is associated with greater levels of childhood CSA (Crosnoe et al., 2010). Other research has reported that childhood CSA may be a mediating factor in associations between SES and neurocognitive function.(Rosen et al., 2020, 2018) Nevertheless, there is also evidence that low-SES children benefit more from childhood CSA than higher-SES children(Crosnoe et al., 2010), suggesting a more complex relationship between CSA and SES, and their potential effects on neurocognitive change in adulthood. Future studies would benefit from investigating whether childhood CSA moderates associations between changes in brain structure and cognitive in adulthood above and beyond effects of childhood SES. Furthermore, some analyses were limited by relatively small sample sizes, such as in the case of DTI measures, which may account for the unexpected finding that higher CSA was marginally predictive of a stronger relationship between FA and change in speed performance over time. As the follow-up visits are still ongoing for the study, we expect to revisit the analyses with a larger sample size in the future. It is also important to note that although we used a validated questionnaire to measure childhood CSA, self-report questionnaires are susceptible to reporter inaccuracy, particularly when assessing activity that occurred years prior to the time of assessment, and potential effects of recall bias should be considered in interpreting the current results. Lastly, although we controlled for effects of age in our analyses, the wide age range included in relatively small sample sizes may obscure potential smaller effects of childhood CSA on brain structure and cognitive performance.

5. Conclusions

In a cohort of healthy adults, greater engagement in cognitively stimulating activities during childhood predicted a weaker relationship between brain structure and cognitive performance at baseline. Longitudinally, childhood CSA attenuated effects of changes in structure on decline in cognitive function over an average of 5 years, suggesting cognitive engagement early life may confer cognitive reserve that protects against the potential negative effects of brain changes on cognition later in life.

Funding/Support

This study was funded by the National Institute on Aging (AG061008, AG026158, AG038465).

Verification

The authors verify that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

CRediT authorship contribution statement

Yaakov Stern: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Yian Gu:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Reshma S. Babukutty:** Data curation, Writing – review & editing. **Christian Habeck:** Data curation, Methodology, Writing – review & editing. **Yunglin Gazes:** Data curation, Methodology, Writing – review & editing. **Caleb R. Haynes:** Data curation, Writing – review & editing. **Alexandra M. Gaynor:** Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft.

Declaration of Competing Interest

None.

Data Availability

Data used in this study are available upon request to the corresponding author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.02.010.

References

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 125, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019.

Arenaza-Urquijo, E.M., Landeau, B., La Joie, R., Mevel, K., Mézenge, F., Perrotin, A., Desgranges, B., Bartrés-Faz, D., Eustache, F., Chételat, G., 2013. Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. NeuroImage 83, 450–457. https://doi.org/10.1016/j.neuroimage.2013.06.053.

Baldivia, B., Andrade, V.M., Bueno, O.F.A., 2008. Contribution of education, occupation and cognitively stimulating activities to the formation of cognitive reserve. Dement. Neuropsychol. 2, 173–182. https://doi.org/10.1590/S1980-57642009DN20300003.

Barulli, D., Stern, Y., 2013. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends in Cognit. Sci. 17 https://doi.org/10.1016/j.tics.2013.08.012.

Barulli, D.J., Rakitin, B.C., Lemaire, P., Stern, Y., 2013. The influence of cognitive reserve on strategy selection in normal aging. J. Int. Neuropsychol. Soc. 19, 841–844. https://doi.org/10.1017/S1355617713000593.

Becker, J.T., Mintun, M.A., Aleva, K., Wiseman, M.B., Nichols, T., DeKosky, S.T., 1996. Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. Neurology 46, 692–700. https://doi.org/10.1212/wnl.46.3.692.

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Leon, C.F.M., de, Arnold, S.E., Barnes, L.L., Bienias, J.L., 2003. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 60, 1909–1915. https://doi.org/10.1212/01.WNL.0000069923.64550.9F.

Bennett, D.A., Schneider, J.A., Wilson, R.S., Bienias, J.L., Arnold, S.E., 2005. Education modifies the association of amyloid but not tangles with cognitive function. Neurology 65, 953–955. https://doi.org/10.1212/01.wnl.0000176286.17192.69.

Brickman, A.M., Siedlecki, K.L., Muraskin, J., Manly, J.J., Luchsinger, J.A., Yeung, L.-K., Brown, T.R., DeCarli, C., Stern, Y., 2011. White matter hyperintensities and cognition. Test. Reserve Hypothes. Neurobiol. Aging 32, 1588–1598. https://doi.org/10.1016/j.neurobiolaging.2009.10.013.

Brown, J., Cooper-Kuhn, C.M., Kempermann, G., Van Praag, H., Winkler, J., Gage, F.H., Kuhn, H.G., 2003. Enriched environment and physical activity stimulate

hippocampal but not olfactory bulb neurogenesis. Eur. J. Neurosci. 17, 2042–2046. https://doi.org/10.1046/j.1460-9568.2003.02647.x.
Buschke, H., Fuld, P.A., 1974. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 24. https://doi.org/10.1212/WNL.24.11.1019, 1019–1019.
Cedres, N., Diaz-Galvan, P., Diaz-Flores, L., Muehlboeck, J.-S., Molina, Y., Barroso, J., Westman, E., Ferreira, D., 2021. The interplay between gray matter and white matter neurodegeneration in subjective cognitive decline. Aging 13, 19963–19977. https://doi.org/10.18632/aging.203467.
Chapko, D., McCormack, R., Black, C., Staff, R., Murray, A., 2018. Life-course determinants of cognitive reserve (CR) in cognitive aging and dementia – a systematic literature review. Aging Ment. Health 22, 921–932. https://doi.org/10.1080/13607863.2017.1348471.
Chen, Y., Lv, C., Li, X., Zhang, J., Chen, K., Liu, Z., Li, H., Fan, J., Qin, T., Luo, L., Zhang, Z., 2019. The positive impacts of early-life education on cognition, leisure activity, and brain structure in healthy aging. Aging 11, 4923–4942. https://doi.org/10.18632/aging.102088.
Chodosh, J., Reuben, D.B., Albert, M.S., Seeman, T.E., 2002. Predicting cognitive impairment in high-functioning community-dwelling older persons: MacArthur studies of successful aging. J. Am. Geriatr. Soc. 50, 1051–1060. https://doi.org/10.1046/j.1532-5415.2002.50260.x.
Christensen, H., Korten, A.E., Jorm, A.F., Henderson, A.S., Jacomb, P.A., Rodgers, B., Mackinnon, A.J., 1997. Education and decline in cognitive performance: compensatory but not protective. Int. J. Geriatr. Psychiatr. 12, 323–330. https://doi.org/10.1002/(sici)1099-1166(199703)12:3<323::aid-gps492>3.0.co;2-n.
Christensen, H., Anstey, K.J., Parslow, R.A., Maller, J., Mackinnon, A., Sachdev, P., 2006. The brain reserve hypothesis, brain atrophy and aging. Gerontology 53, 82–95. https://doi.org/10.1159/000096482.
Cox, S.R., Dickie, D.A., Ritchie, S.J., Karama, S., Pattie, A., Royle, N.A., Corley, J., Aribisala, B.S., Hernández, M.V., Maniega, S.M., Starr, J.M., Bastin, M.E., Evans, A. C., Wardlaw, J.M., Deary, I.J., 2016. Associations between education and brain structure at age 73 years, adjusted for age 11 IQ. Neurology 87, 1820–1826. https://doi.org/10.1212/WNL.0000000000003247.
Crosnoe, R., Leventhal, T., Wirth, R.J., Pierce, K.M., Pianta, R.C., NICHD Early Child Care Research Network, 2010. Family socioeconomic status and consistent environmental stimulation in early childhood. Child Dev. 81, 972–987. https://doi.org/10.1111/j.1467-8624.2010.01446.x.
Czernochowski, D., Fabiani, M., Friedman, D., 2008. Use it or lose it? SES mitigates age-related decline in a recency/recognition task. Neurobiol. Aging 29, 945–958. https://doi.org/10.1016/j.neurobiolaging.2006.12.017.
Dekhtyar, S., Wang, H.-X., Scott, K., Goodman, A., Koupil, I., Herlitz, A., 2015. A life-course study of cognitive reserve in dementia—from childhood to old age. Am. J. Geriatr. Psychiatr. Longitud. Stud. 23, 885–896. https://doi.org/10.1016/j.jagp.2015.02.002.
Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.
Ecker, C., Stahl, D., Daly, E., Johnston, P., Thomson, A., Murphy, D.G.M., 2009. Is there a common underlying mechanism for age-related decline in cortical thickness? NeuroReport 20, 1155. https://doi.org/10.1097/WNR.0b013e32832ec181.
Everson-Rose, S.A., Mendes de Leon, C.F., Bienias, J.L., Wilson, R.S., Evans, D.A., 2003. Early life conditions and cognitive functioning in later life. Am. J. Epidemiol. 158, 1083–1089. https://doi.org/10.1093/aje/kwg263.
Fjell, A.M., Walhovd, K.B., 2010. Structural brain changes in aging: courses, causes and cognitive consequences. Rev. Neurosci. 21 https://doi.org/10.1515/REVNEURO.2010.21.3.187.
Foubert-Samier, A., Catheline, G., Amieva, H., Dilharreguy, B., Helmer, C., Allard, M., Dartigues, J.-F., 2012. Education, occupation, leisure activities, and brain reserve: a population-based study. Neurobiol. Aging 33, 423.e15–423.e25. https://doi.org/10.1016/j.neurobiolaging.2010.09.023.
Gazes, Y., Lee, S., Fang, Z., Mensing, A., Noofoory, D., Hidalgo Nazario, G., Babukutty, R., Chen, B.B., Habeck, C., Stern, Y., 2023. Effects of brain maintenance and cognitive reserve on age-related decline in three cognitive abilities. J. Gerontol. Ser. B, gbad044. https://doi.org/10.1093/geronb/gbad044.
Golden, C., Freshwater, S.M., Golden, Z., 2012. Stroop Color and Word. Test. https://doi.org/10.1037/t06065-000.
Hanson, J.L., Adluru, N., Chung, M.K., Alexander, A.L., Davidson, R.J., Pollak, S.D., 2013. Early neglect is associated with alterations in white matter integrity and cognitive functioning. Child Dev. 84, 1566–1578. https://doi.org/10.1111/cdev.12069.
Herrera, E.J., Caramelli, P., Silveira, A.S.B., Nitrini, R., 2002. Epidemiologic Survey of Dementia in a Community-Dwelling Brazilian Population. Alzheimer Disease Associated Disorders 16, 103.
Hirase, H., Shinohara, Y., 2014. Transformation of cortical and hippocampal neural circuit by environmental enrichment. Neuroscience 280, 282–298. https://doi.org/10.1016/j.neuroscience.2014.09.031.
Kaplan, G.A., Turrell, G., Lynch, J.W., Everson, S.A., Helkala, E.-L., Salonen, J.T., 2001. Childhood socioeconomic position and cognitive function in adulthood. Int. J. Epidemiol. 30, 256–263. https://doi.org/10.1093/ije/30.2.256.
Karama, S., Ad-Dab'bagh, Y., Haier, R.J., Deary, I.J., Lyttelton, O.C., Lepage, C., Evans, A.C., 2009. Positive association between cognitive ability and cortical thickness in a representative US sample of healthy 6 to 18 year-olds. Intell. Intell. Brain 37, 145–155. https://doi.org/10.1016/j.intell.2008.09.006.
Kellner, E., Dhital, B., Kiselev, V.G., Reisert, M., 2016. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn. Reson. Med. 76, 1574–1581. https://doi.org/10.1002/mrm.26054.
Kramer, A.F., Bherer, L., Colcombe, S.J., Dong, W., Greenough, W.T., 2004. Environmental influences on cognitive and brain plasticity during aging. J. Gerontol. Ser. A 59, M940–M957. https://doi.org/10.1093/gerona/59.9.M940.
Le Carret, N., Lafont, S., Letenneur, L., Dartigues, J.-F., Mayo, W., Fabrigoule, C., 2003. The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve. Dev. Neuropsychol. 23, 317–337. https://doi.org/10.1207/S15326942DN2303_1.
Lesuis, S.L., Hoeijmakers, L., Korosi, A., de Rooij, S.R., Swaab, D.F., Kessels, H.W., Lucassen, P.J., Krugers, H.J., 2018. Vulnerability and resilience to Alzheimer's disease: early life conditions modulate neuropathology and determine cognitive reserve. Alzheimer's Res. Ther. 10, 95. https://doi.org/10.1186/s13195-018-0422-7.
Manly, J.J., Touradji, P., Tang, M.-X., Stern, Y., 2003. Literacy and memory decline among ethnically diverse elders. J. Clin. Exp. Neuropsychol 25, 680–690. https://doi.org/10.1076/jcen.25.5.680.14579.
Montemurro, S., Filippini, N., Ferrazzi, G., Mantini, D., Arcara, G., Marino, M., 2023. Education Differentiates Cognitive Performance and Resting State Fmri Connectivity in Healthy Aging. https://doi.org/10.1101/2023.02.22.529483.
Mooij, S.M.M., de, Henson, R.N.A., Waldorp, L.J., Kievit, R.A., 2018. Age differentiation within gray matter, white matter, and between memory and white matter in an adult life span cohort. J. Neurosci. 38, 5826–5836. https://doi.org/10.1523/JNEUROSCI.1627-17.2018.
Mukadam, N., Sommerlad, A., Huntley, J., Livingston, G., 2019. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. Lancet Glob. Health 7, e596–e603. https://doi.org/10.1016/S2214-109X(19)30074-9.
Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends in Cognit. Sci. 16, 292–305. https://doi.org/10.1016/j.tics.2012.04.005.
Raz, N., Ghisletta, P., Rodrigue, K.M., Kennedy, K.M., Lindenberger, U., 2010. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. Neuroimage 51, 501–511. https://doi.org/10.1016/j.neuroimage.2010.03.020.
Reitan, R.M., 1971. Trail Making Test: Manual for Administration and Scoring. Reitan Neuropsychological Laboratory, Tuscon, AZ.
Rentz, D.M., Locascio, J.J., Becker, J.A., Moran, E.K., Eng, E., Buckner, R.L., Sperling, R. A., Johnson, K.A., 2010. Cognition, reserve, and amyloid deposition in normal aging. Ann. Neurol. 67, 353–364. https://doi.org/10.1002/ana.21904.
Rogers, M.A.M., Plassman, B.L., Kabeto, M., Fisher, G.G., McArdle, J.J., Llewellyn, D.J., Potter, G.G., Langa, K.M., 2009. Parental education and late-life dementia in the United States. J. Geriatr. Psychiatry. Neurol. 22, 71–80. https://doi.org/10.1177/0891988708328220.
Rosen, M.L., Sheridan, M.A., Sambrook, K.A., Meltzoff, A.N., McLaughlin, K.A., 2018. Socioeconomic disparities in academic achievement: a multi-modal investigation of neural mechanisms in children and adolescents. NeuroImage 173, 298–310. https://doi.org/10.1016/j.neuroimage.2018.02.043.
Rosen, M.L., Hagen, M.P., Lurie, L.A., Miles, Z.E., Sheridan, M.A., Meltzoff, A.N., McLaughlin, K.A., 2020. Cognitive stimulation as a mechanism linking socioeconomic status with executive function: a longitudinal investigation. Child Dev. 91, e762–e779. https://doi.org/10.1111/cdev.13315.
Sale, A., Berardi, N., Maffei, L., 2014. Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol. Rev. 94, 189–234. https://doi.org/10.1152/physrev.00036.2012.
Salthouse, T.A., Habeck, C., Razlighi, Q., Barulli, D., Gazes, Y., Stern, Y., 2015. Breadth and age-dependency of relations between cortical thickness and cognition. Neurobiol. Aging 36, 3020–3028. https://doi.org/10.1016/j.neurobiolaging.2015.08.011.
Scarmeas, N., Zarahn, E., Anderson, K.E., Habeck, C.G., Hilton, J., Flynn, J., Marder, K.S., Bell, K.L., Sackeim, H.A., Van Heertum, R.L., Moeller, J.R., Stern, Y., 2003. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. Arch. Neurol. 60, 359–365. https://doi.org/10.1001/archneur.60.3.359.
Stern, Y., 2009. Cognitive reserve. Neuropsychologia 47, 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004.
Stern, Y., Alexander, G.E., Prohovnik, I., Mayeux, R., 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann. Neurol. 32, 371–375. https://doi.org/10.1002/ana.410320311.
Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M.X., Wilder, D., Mayeux, R., 1994. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 271, 1004–1010. https://doi.org/10.1001/jama.1994.03510370056032.
Stern, Y., Albert, S., Tang, M.-X., Tsai, W.-Y., 1999. Rate of memory decline in AD is related to education and occupation: cognitive reserve?, 1942–1942 Neurology 53. https://doi.org/10.1212/WNL.53.9.1942.
Stern, Y., Habeck, C., Steffener, J., Barulli, D., Gazes, Y., Razlighi, Q., Shaked, D., Salthouse, T., 2014. The reference ability neural network study: motivation, design, and initial feasibility analyses. Neuroimage 103, 139–151. https://doi.org/10.1016/j.neuroimage.2014.09.029.
Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J., Habeck, C., 2018. A task-invariant cognitive reserve network. NeuroImage 178, 36–45. https://doi.org/10.1016/j.neuroimage.2018.05.033.
Stern, Y., Varangis, E., Habeck, C., 2021. A framework for identification of a resting-bold connectome associated with cognitive reserve. NeuroImage 232, 117875. https://doi.org/10.1016/j.neuroimage.2021.117875.

Teipel, S.J., Bokde, A.L.W., Meindl, T., Amaro, E., Soldner, J., Reiser, M.F., Herpertz, S. C., Möller, H.-J., Hampel, H., 2010. White matter microstructure underlying default mode network connectivity in the human brain. NeuroImage 49, 2021–2032. https://doi.org/10.1016/j.neuroimage.2009.10.067.

Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., Gee, J.C., 2010. N4ITK: improved N3 bias correction. IEEE Trans Med. Imag. 29, 1310–1320. https://doi.org/10.1109/TMI.2010.2046908.

Valenzuela, M., Sachdev, P., 2009. Can cognitive exercise prevent the onset of dementia? systematic review of randomized clinical trials with longitudinal follow-up. Am. J. Geriatr. Psychiatr. 17, 179–187. https://doi.org/10.1097/JGP.0b013e3181953b57.

Valenzuela, M.J., Sachdev, P., 2006. Brain reserve and cognitive decline: a non-parametric systematic review. Psychol. Med. 36, 1065–1073. https://doi.org/10.1017/S0033291706007744.

Valenzuela, M.J., Matthews, F.E., Brayne, C., Ince, P., Halliday, G., Kril, J.J., Dalton, M. A., Richardson, K., Forster, G., Sachdev, P.S., 2012. Multiple biological pathways link cognitive lifestyle to protection from dementia. Biol. Psychiatr. 71, 783–791. https://doi.org/10.1016/j.biopsych.2011.07.036.

Veraart, J., Novikov, D.S., Christiaens, D., Ades-aron, B., Sijbers, J., Fieremans, E., 2016. Denoising of diffusion MRI using random matrix theory. NeuroImage 142, 394–406. https://doi.org/10.1016/j.neuroimage.2016.08.016.

Wechsler, D., 1987. WMS-R: Wechsler Memory Scale-Revised. Psychological Corporation, San Antonio, TX.

Wechsler, D., 1997. Administration and Scoring Manual for the WAIS-III. Psychological Corporation, San Antonio, TX.

Westlye, L.T., Grydeland, H., Walhovd, K.B., Fjell, A.M., 2011. Associations between regional cortical thickness and attentional networks as measured by the attention network test. Cereb. Cortex 21, 345–356. https://doi.org/10.1093/cercor/bhq101.

Wilson, R., Barnes, L., Bennett, D., 2003. Assessment of lifetime participation in cognitively stimulating activities. J. Clin. Exp. Neuropsychol. 25, 634–642. https://doi.org/10.1076/jcen.25.5.634.14572.

Wilson, R.S., Bennett, D.A., Bienias, J.L., Aggarwal, N.T., Leon, C.F.M., de, Morris, M.C., Schneider, J.A., Evans, D.A., 2002a. Cognitive activity and incident AD in a population-based sample of older persons. Neurology 59, 1910–1914. https://doi.org/10.1212/01.WNL.0000036905.59156.A1.

Wilson, R.S., Mendes de Leon, C.F., Barnes, L.L., Schneider, J.A., Bienias, J.L., Evans, D. A., Bennett, D.A., 2002b. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 287, 742–748. https://doi.org/10.1001/jama.287.6.742.

Wilson, R.S., Barnes, L.L., Krueger, K.R., Hoganson, G., Bienias, J.L., Bennett, D.A., 2005. Early and late life cognitive activity and cognitive systems in old age. J. Int. Neuropsychol. Soc. 11, 400–407. https://doi.org/10.1017/S1355617705050459.

Wilson, R.S., Scherr, P.A., Schneider, J.A., Tang, Y., Bennett, D.A., 2007. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology 69, 1911–1920. https://doi.org/10.1212/01.wnl.0000271087.67782.cb.

Wilson, R.S., Boyle, P.A., Yu, L., Barnes, L.L., Schneider, J.A., Bennett, D.A., 2013. Life-span cognitive activity, neuropathologic burden, and cognitive aging. Neurology 81, 314–321. https://doi.org/10.1212/WNL.0b013e31829c5e8a.

Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zöllei, L., Augustinack, J., Wang, R., Salat, D., Ehrlich, S., Behrens, T., Jbabdi, S., Gollub, R., Fischl, B., 2011. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Front. Neuroinf. 5.