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Research Article

Cortical Surface Area Profile Mediates Effects of Childhood Disadvantage on Later-Life General Cognitive Ability

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Abstract

Objectives: Abstract Childhood disadvantage is associated with lower general cognitive ability (GCA) and brain structural differences in midlife and older adulthood. However, the neuroanatomical mechanisms underlying childhood disadvantage effects on later-life GCA remain poorly understood. Although total surface area (SA) has been linked to lifespan GCA differences, total SA does not capture the nonuniform nature of childhood disadvantage effects on neuroanatomy, which varies across unimodal and transmodal cortices. Here, we examined whether cortical SA profile—the extent to which the spatial patterning of SA deviates from the normative unimodal–transmodal cortical organization—is a mediator of childhood disadvantage effects on later-life GCA.

Methods: In 477 community-dwelling men aged 56–72 years old, childhood disadvantage index was derived from four indicators of disadvantages and GCA was assessed using a standardized test. Cortical SA was obtained from structural magnetic resonance imaging. For cortical SA profile, we calculated the spatial similarity between maps of individual cortical SA and MRI-derived principal gradient (i.e., unimodal–transmodal organization). Mediation analyses were conducted to examine the indirect effects of childhood disadvantage index through cortical SA profile on GCA.

Results: Around 1.31% of childhood disadvantage index effects on later-life GCA were mediated by cortical SA profile, whereas total SA did not. Higher childhood disadvantage index was associated with more deviation of the cortical SA spatial patterning from the principal gradient, which in turn related to lower later-life GCA.

Discussion: Childhood disadvantage may contribute to later-life GCA differences partly by influencing the spatial patterning of cortical SA in a way that deviates from the normative cortical organizational principle.

Keywords: Association cortices, Cortical organization, Neurodevelopment, Transmodal, Unimodal

Exposures to childhood disadvantage have enduring consequences for cognitive and brain outcomes across the lifespan. Forms of childhood disadvantage often include socioeconomic (e.g., low SES, poverty), psychological (e.g., family disruptions, trauma), and environmental risks (e.g., crowding, neighborhood crime; McLaughlin et al., 2014; Tooley et al., 2021). Accumulating evidence suggests that early-life disadvantages become biologically embedded in the brain during critical periods of development and are linked to individual differences in cognition during childhood and adolescence (Noble & Giebler, 2020; Sydnor et al., 2021; Tooley et al., 2021). Strikingly, the association between childhood disadvantage and cognition has been shown to persist into midlife and older adulthood, with childhood disadvantage relating to both lower general cognitive ability (GCA) and poorer performance across multiple cognitive domains (Beck et al., 2018; Lyu & Burr, 2015). Likewise, the associations between childhood disadvantage and later-life (age >45 years) brain morphometry of gray and white matter suggest its scarring imprint on brain structure across the lifespan (De Looze et

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al., 2023; Loued-Khenissi et al., 2022; Staff et al., 2012). Nonetheless, the neuroanatomical mechanisms underlying childhood disadvantage effects on later-life cognitive function remain poorly understood, particularly in late midlife and older adulthood.

GCA (e.g., IQ) reflects an individual's overall cognitive function, which remains relatively stable throughout adulthood despite some aging-related decline (Deary et al., 2012; Lyons et al., 2009). Although behavioral mediators of childhood disadvantage effects on later-life GCA have been identified (Beck et al., 2018; Zhang et al., 2020), the neuroanatomical mediators remain elusive. Converging evidence has suggested the neurodevelopmental origins of individual differences in cognition such as GCA (Fjell, Grydeland, et al., 2015; Kovacs et al., 2014; Walhovd et al., 2016). For instance, cortical surface area (SA) has been consistently linked to GCA (Fjell, Westlye, et al., 2015; Vuoksimaa et al., 2015) and cortical regions whose SA is associated with GCA in children, continue to underpin GCA across young and older adulthood (Walhovd et al., 2016). These results suggest that brain-cognition links that appear early in life may remain fairly stable across the lifespan. Most of these GCA-related cortical regions are located within the association cortices (e.g., prefrontal, inferior parietal areas) that are known to undergo a protracted period of development, during which they are highly susceptible to environmental influences (Larsen et al., 2023; Sydnor et al., 2021). Indeed, childhood disadvantage appears to preferentially affect the development of association cortices (e.g., areal expansion) in children and adolescents (Larsen et al., 2023; Sydnor et al., 2021; Tooley et al., 2021). These impacts on brain development and maturation may, therefore, contribute to individual differences in GCA across the lifespan. A large-scale UK Biobank study supports this hypothesis by showing that later-life total SA mediates 1.19% of childhood disadvantage effects (i.e., abuse, stress) on general intelligence (i.e., g-factor) in individuals 40–69 years old (Williams et al., 2023). However, total SA does not capture development-linked regional variability of SA across the cortex. Such regional variability may thus account for more variance than total SA with respect to the association between childhood disadvantage and GCA.

Cortical development is spatially and temporally variable across the cortex and has been shown to vary along a principal axis of cortical organization that spans from lower-order, unimodal primary sensory and motor regions to transmodal, higher-order association regions (Larsen et al., 2023; Sydnor et al., 2021). For instance, there is greater developmental SA expansion of transmodal association cortices than that of unimodal primary sensorimotor cortices from infancy to adulthood (Hill et al., 2010). The principal axis of cortical organization has been found across different neuroimaging datatypes (e.g., microstructural, functional, metabolic), reflecting the existence of an overarching organizational principle of the human cortex that is heavily implicated in cortical development (Sydnor et al., 2021). For instance, the principal functional gradient derived from functional connectivity quantifies the spatial embedding of cortical functional organization (i.e., unimodal–transmodal; Margulies et al., 2016) and has been shown to undergo development-linked spatial shifts from childhood to adolescence (Dong et al., 2021). Specifically, the transition from childhood to adolescence is marked by shifts from a unimodal-dominant organization that separates primary sensorimotor cortices from each other to an adult-like unimodal–transmodal organization that separates primary cortices from association cortices implicated in higher-order cognitive functions (Dong et al., 2021). A study in adolescents showed that childhood environmental effects (e.g., poverty, neighborhood crowding) on brain functional development vary across unimodal and transmodal regions, suggesting nonuniform susceptibility to environmental effects across the cortex (Sydnor et al., 2023). Thus, it is possible that childhood disadvantage effects on cortical SA are also patterned and may be differentially expressed along the development-linked principal functional gradient. Because childhood disadvantage negatively impacts typical neurodevelopment, we hypothesized the extent to which an individual's spatial patterning or spatial profile of cortical SA deviates from the normative adult-like principal functional gradient of cortical organization (i.e., negatively correlated), may reflect disadvantage-linked effects on brain maturation, thereby contributing to individual differences in later-life GCA.

However, to our knowledge, there have been no studies examining the spatial profile of cortical SA in relation to either childhood disadvantage or GCA in late midlife and older adulthood. Nor has prior work examined the spatial profile of cortical SA as a mediator of the childhood disadvantage-GCA association. In the present study, we addressed these questions in 477 community-dwelling men aged 56 to 72 years old (Kremen, Franz, et al., 2019). Across the cortex, we first mapped the associations between childhood disadvantage, which encompasses socioeconomic and environmental disadvantages prior to the age of 18, and regional cortical SA. We then examined whether these associations are patterned such that they exhibit significant spatial correspondence to the principal functional gradient. Next, we investigated whether childhood disadvantage predicts individual differences in the spatial profile of cortical SA (i.e., similarity to the principal gradient), and whether the spatial profile predicts later-life GCA. Finally, we conducted mediation analyses to explore individual spatial profiles of cortical SA as a neuroanatomical mediator of childhood disadvantage effects on later-life GCA.

Method

Participants

Participants were from the Vietnam Era Twin Study of Aging (VETSA), a multisite ongoing longitudinal study of aging and risk for Alzheimer's disease beginning in middle age (Kremen, Franz, et al., 2019). They are similar to American men in their age cohort with respect to health, education, and lifestyle characteristics (Schoenborn & Heyman, 2009). For the present study, a total of 477 community-dwelling men (mean age = 63.37 years, standard deviation [*SD*] = 3.64; range = 56–72) from Wave 2 and Wave 3 of the study were included. Our focus is on the effects of childhood disadvantage on individual differences in later-life GCA; the latter remains relatively stable across much of adulthood (Lyons et al., 2017). Therefore, we only included one wave of neuroimaging and cognitive assessments from each participant in the analyses (i.e., cross-sectional). Specifically, we used data from the first assessment during which an individual had available imaging data acquired on a 3T MRI scanner. Participants traveled to the University of California, San Diego (UCSD) or Boston University to participate in the VETSA. Informed consent was obtained from all participants and institutional

Table 1. Characteristics of the Study Sample ($N = 477$)

Characteristics	Mean (*SD*)	*N* (%)	Range
Age	63.37 (3.64)		55.96–71.72
Years of education	13.91 (2.06)		8.00–20.00
Childhood disadvantage index[a]	1.42 (1.14)		0.00–4.00
Level			
0		118 (26%)	
1		135 (29%)	
2		125 (27%)	
3		62 (13%)	
4		20 (4%)	
General cognitive ability (*z*-scores)[b]	0.30 (0.68)		−2.06–2.05
Father socioeconomic status[a]	34.00 (11.75)		8.00–66.00
Father occupation[a]	4.71 (1.77)		0.00–9.00
Father education[a]	10.60 (3.33)		0.00–20.00
Mother education[a]	11.17 (2.51)		0.00–18.00
Cognitive status[a]			
Cognitively unimpaired		404 (86%)	
Mild cognitive impairment		65 (14%)	

[a]Missing: childhood disadvantage index ($n = 17$), father SES ($n = 7$), father occupation ($n = 7$), father education ($n = 5$), mother education ($n = 2$), cognitive status ($n = 8$).
[b]The *z*-scores were transformed from percentiles and the mean *z*-scores for the full sample are equivalent to an IQ of approximately 105.

review boards at both sites approved all protocols. Table 1 is a summary of the sample characteristics.

Cognitive Status

Cognitive status was determined based on previously published criteria from our group (Williams et al., 2021). Briefly, the Jak–Bondi approach was used to diagnose mild cognitive impairment (MCI; Bondi et al., 2008; Jak et al., 2009). Participants completed a neuropsychological battery comprising 18 tests that encompassed 6 cognitive domains. Criteria for impairment within a domain required performance on 2+ tests that were each >1.5 *SD*s below age- and education-adjusted normative means.

Childhood Disadvantage Index

A previously developed composite index of childhood disadvantage based on interview and questionnaire data about family history from the VETSA participants was used (Franz et al., 2013). Specifically, the childhood disadvantage index (CDI) included 4 indicators of childhood disadvantage: (1) low SES father, (2) mother not completing high school (<12 years education), (3) family disruption (separation from either or both parents for most of childhood prior to age 18 due to factors such as parental death, incapacity, separation, or divorce), and (4) large family size. These 4 indicators are comparable to indicators used in the Isle of Wight studies (Rutter & Quenton, 1977; Rutter et al., 1976), with the exception of paternal criminality and maternal mental disorder, which were not available in the VETSA data set (Franz et al., 2013).

Each of the 4 indicators of childhood disadvantage was defined dichotomously (0/1; absent/present) based on the criteria below. Father SES was calculated using the Hollingshead and Redlich scales (Hollingshead & Redlich, 1955), which provides a weighted formula that combines occupation and education to compute SES. According to the Hollingshead and Redlich scales, occupation was coded on a 0–9 scale (0 = homemaker/unemployed/retired; 1 = unskilled laborer; 9 = major professionals), and education was recoded to a 1–7 scale (1 = none to seventh grade to 7 = graduate professional training). Next, based on the weighted formula (Hollingshead & Redlich, 1955), an SES composite score was then calculated as: (occupation score × 5) + (education score × 3). Participants with father SES less than or equal to 32 were considered to have a low SES father, which reflects a combination of less than high school education and semi-skilled manual occupation or lower (Franz et al., 2013). For mother education, participants with a mother who did not complete high school (<12 years of education) were coded as 1 and those who had a mother with greater than or equal to 12 years of education were coded as 0. Family disruption was coded as 1 for those who separated from either or both of parents for most of childhood prior to age 18 and 0 for those who did not experience separation. Large family size was defined as families in the top quartile of the full sample, which corresponded to a family size greater than 5 children. Participants who came from a family with greater than five children were coded as 1 and those from a family with less than or equal to five children were coded as 0. Finally, the CDI was calculated for each participant by summing all four dichotomous variables, with higher scores representing more disadvantages. Detailed rationale is described in Supplementary Material.

General Cognitive Ability

The Armed Forces Qualification Test (AFQT) is a standardized, validated 100-item multiple-choice paper-and-pencil test of GCA (Kremen, Beck, et al., 2019). It includes four components: vocabulary, arithmetic, spatial processing, and knowledge and reasoning about tools. This test is highly correlated with other tests of GCA such as the Wechsler Adult Intelligence Scale ($r = 0.84$) and is very stable ($r = 0.73$ across a test–retest interval of 42 years; Kremen, Beck, et al., 2019; Lyons et al., 2017). In this study, we used the AFQT percentile

scores based on half of the items (50 items) from the AFQT, as we shortened the test at Wave 3 due to participant's older age and to minimize testing fatigue. The AFQT percentile scores were probit transformed and *z*-scored for analysis. The mean *z*-score of 0.30 thus corresponds to an IQ of approximately 105.

MRI Acquisition and Processing

Images were acquired at UCSD ($N = 341$) and MGH ($N = 136$). At UCSD, T1-weighted (3D fast spoiled gradient echo, TR = 8.084 ms, TE = 3.164 ms) images were acquired on two 3T GE Discovery 750× scanners (GE Healthcare, Waukesha, WI) with an eight-channel phased array head coil. At MGH, T1-weighted (3D magnetization-prepared rapid gradient echo, TR = 2170 ms, TE = 4.33 ms images TR = 9500 ms, TE = 94 ms) were acquired with a 3T Siemens Tim Trio (Siemens USA, Washington, DC) with a 32-channel head coil.

All images were preprocessed at the UCSD Center for Multimodal Imaging and Genetics as described previously (Eyler et al., 2012; Kremen, Beck, et al., 2019). All raw and processed MRI images were visually inspected to exclude data with severe scanner artifacts or excessive head motion. The cortical surface was reconstructed to assess SA using the FreeSurfer version 6.0 (surfer.nmr.mgh.harvard.edu) software package. Briefly, the T1-weighted images were corrected for gradient nonlinearity distortions and B1 field inhomogeneity, underwent removal of the skull (nonbrain) and were resampled and registered to standard space (MNI 305). Boundaries between gray matter, white matter, and cerebrospinal fluid were defined. The cortical surface model was manually reviewed and edited for technical accuracy. Minimal manual editing was performed by applying standard, objective editing rules (see Supplementary Material). To calculate parcel-wise SA for each participant, the cortical SA map was resampled to the FreeSurfer spherical atlas space, and the Schaefer 400 parcellation scheme (Schaefer et al., 2018) was used to divide the cortical surface into 400 parcels.

Brain Map of Principal Functional Gradient of Cortical Organization

The group-level brain map of the principal functional gradient was derived based on resting state functional connectivity data from 820 participants in the Human Connectome Project as described previously (Margulies et al., 2016) and was obtained from neuromaps (Markello et al., 2022). The group-level principal functional gradient map was then parcellated into 400 parcels for comparing with individual and group-level cortical SA maps in VETSA. Positive values of the group-level principal functional gradient map reflect more transmodal-like parcels (e.g., association cortices) and negative gradient values reflect more unimodal-like parcels (e.g., sensorimotor cortices).

Statistical Analyses

All statistical analyses were performed using R version 4.3.1, with the exception of spatial correlations and permutation tests, which were performed using the BrainStat toolbox (Lariviere et al., 2023). Two outliers were winsorized to the nearest minimum or maximum data point. Assumptions of statistical tests were checked. Data distributions of key variables are shown in Supplementary Figures 1–3.

Generating map of childhood disadvantage effect on cortical surface area

To compute and generate a group-level map for the effect of childhood disadvantage on SA, we built a linear mixed model for each of the 400 cortical parcels with CDI as the predictor and cortical SA as the dependent variable. Age and scanner were included as covariates in all models to account for potential effect of age and scanner differences on SA. Twin pair family ID was included as a random intercept in all models to account for correlated outcomes within pairs. The standardized beta coefficient of CDI for each parcel was extracted to index the magnitude of CDI effect on SA. We then projected these standardized beta coefficient values onto the cortical surface, yielding a group-level map.

Spatial correlations and permutation tests

Spatial correlations among group-level brain maps (i.e., principal functional gradient, childhood disadvantage effect on cortical SA) were determined by correlating the values across all parcels (i.e., standardized beta coefficients, gradient values) between two given brain maps. Because the intrinsic spatial smoothness in brain maps may inflate the significance of their spatial correlation, the statistical significance of these correlation coefficients was assessed via spatial autocorrelation-preserving permutation tests or "spin tests" (Alexander-Bloch et al., 2018) (see Supplementary Material for details).

Generating individual cortical surface area spatial profile

We first created individual-level cortical SA maps. The SA of each parcel was first corrected for scanner differences across all participants using linear mixed models with a scanner as the predictor. The adjusted or residualized scores of SA from all parcels were then extracted for each participant, yielding a vector of SA per region (i.e., individual SA map). We then correlated each individual's SA map to the principal functional gradient map, obtaining a similarity score (i.e., spatial profile) that is used to represent individual differences in the spatial patterning of cortical SA for each individual.

Mediation analyses

Mediation analyses were performed using Hayes' PROCESS Macro version 4.3 for R (Hayes, 2017), which provides tests of the total, direct, and indirect effects of CDI (the predictor) on later-life GCA (the dependent variable). The individual cortical SA spatial profile served as the mediator of the CDI–GCA association. All paths and their confidence intervals of the mediation model were estimated based on 10 000 bootstrapped samples via the Hayes' methods, which is robust to non-normal distributions. Age and cognitive status (MCI or cognitively unimpaired) were included as covariates in all models. All models also included the twin pair family ID as a random effect to account for the nonindependence of twins within pairs.

Results

Preliminary Analyses

In preliminary correlational analyses using Pearson's correlation or point-biserial correlation among demographic and cognitive variables, higher levels of CDI were associated with less years of education ($r = -0.24$, $p < .0001$) and lower levels of GCA later in life ($r = -0.19$, $p < .0001$; see Supplementary Figure 4).

Consistent with prior studies of the VETSA data set, older age was associated with lower levels of GCA ($r = -0.11$, $p = .0137$). Finally, MCI status was not significantly associated with years of education or CDI ($ps > .05$), but it was negatively associated with GCA ($r = -0.13$, $p = .0053$).

Mapping Childhood Disadvantage Effect on Later-Life Cortical Surface Area

The magnitude and direction of CDI effects on cortical SA are shown in Figure 1. Higher CDI was associated with smaller SA exclusively for parcels located within transmodal association cortices (parcels with at least a small effect size of standardized beta ≤–0.1 [absolute value: 0.1]). Specifically, most of these transmodal parcels were within the frontoparietal control network and the default mode network implicated in higher-order cognitive functions. In contrast, higher CDI was associated with greater SA for unimodal somatomotor network parcels (33% of parcels with standardized beta ≥0.1), with the rest of the parcels located within the association cortices including dorsal attention network (33%), the frontoparietal control network (17%), and the salience/ventral attention network (17%).

Childhood Disadvantage Effects Vary Along the Principal Functional Gradient of Cortical Organization

We examined whether childhood disadvantage effects on cortical SA are differentially expressed along the unimodal–transmodal axis of cortical organization as captured by the principal functional gradient (Figure 2A). Using spatial correlational analyses, we found a negative spatial correspondence between group-level maps of childhood disadvantage effects and the principal functional gradient ($r = -0.37$, $p_{spin} < .0001$). Not only did childhood disadvantage effects on cortical SA vary along this unimodal–transmodal axis, but also the negative impact of childhood disadvantage on parcel-wise SA (i.e., smaller SA with higher CDI, shown in blue) tended to be found in transmodal regions (i.e., positive gradient values) as shown in Figure 2B.

Building on these group-level analyses, we examined whether childhood disadvantage predicts differences in the spatial patterning of cortical SA at the individual level. Specifically, we explored whether higher childhood disadvantage renders an individual's cortical SA spatial profile less similar to the unimodal–transmodal axis of cortical organization. As hypothesized, we detected a significant negative correlation between CDI and individual SA spatial profile ($\beta = -0.13$, $p = .0196$), indicating that individuals with higher childhood disadvantage have a spatial patterning of cortical SA that resembled the principal functional gradient less closely than that of those with less childhood disadvantage (see Supplementary Figure 5). We also examined whether CDI predicts total SA, but did not detect a significant association ($p > .05$).

Individual Cortical Surface Area Spatial Profile and General Cognitive Ability

Extending prior work that examined the association of total SA with a GCA-like measure, we explored whether the individual SA spatial profile is related to individual differences in GCA in later life. That is, whether the individual cortical SA profile is cognitively meaningful and whether its greater alignment with the hierarchical spatial separation of unimodal and transmodal cortices is related to higher later-life GCA. We found that higher spatial similarity of individual cortical SA spatial profiles to the principal functional gradient was associated with higher levels of GCA, but the association was not statistically significant ($\beta = 0.09$, $p = .515$; see Supplementary Figure 6). We conducted additional analyses by examining the association between total SA and GCA and detected a significantly positive association ($\beta = 0.25$, $p < .0001$) that is consistent with prior findings.

Mediation Analyses

We further probed whether the cortical SA spatial profile may serve as a mediator of the effect of childhood disadvantage on later-life GCA. We found that there was a significant total effect (direct plus indirect) between CDI and GCA ($\beta = -0.1809$, 95% CI [–0.1633 to –0.0546]), along with a significant direct effect (i.e., CDI on GCA; $\beta = -0.1679$, 95% CI [–0.1558 to –0.0464]) and a significant indirect effect (i.e., CDI on GCA via SA spatial profile; $\beta = -0.0131$, 95% CI [–0.0305 to –0.0001]; Figure 3) These results indicate that 1.31% of childhood disadvantage effects on later-life GCA were partially mediated by how well an individual's cortical SA spatial profile aligns with the principal functional gradient.

Discussion

Childhood disadvantage can fundamentally shape neurodevelopment, leading to individual differences in cognition and brain that are preserved across the lifespan. In a cohort of community-dwelling late middle-aged and older men, we found that the effects of childhood disadvantage on cortical SA vary along the unimodal–transmodal axis of cortical organization. Regions in which smaller SA is linked to greater disadvantage were observed in association cortices implicated in higher-order cognitive functions. Moreover, we demonstrated that individual differences in the spatial patterning of cortical SA partially mediate the effects of childhood disadvantage

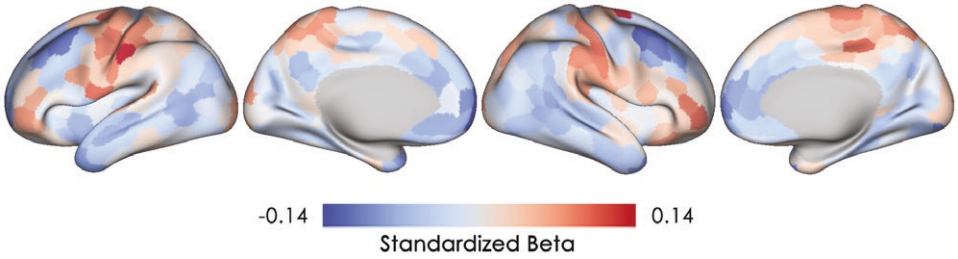

Figure 1. Effect of childhood disadvantage on later-life cortical surface area. Standardized beta coefficients are plotted for all 400 cortical parcels, with cooler color indicating a negative association between childhood disadvantage and surface area and warmer color indicating a positive association.

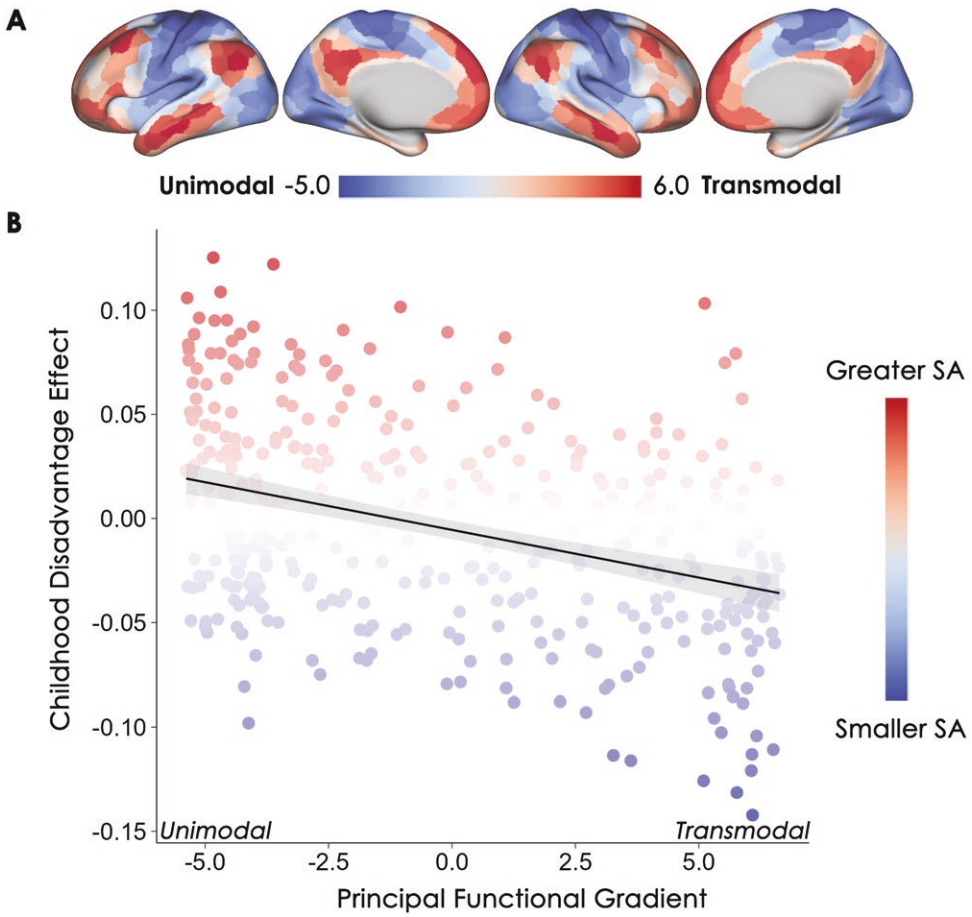

Figure 2. Association of childhood disadvantage effect and principal functional gradient. (**A**) The map of principal functional gradient of cortical macroscale organization based on Schaefer 400, 17-networks parcellation scheme is shown, with warmer color reflecting parcels that are more transmodal-like and cooler color reflecting parcels that are more unimodal-like. (**B**) For all 400 cortical parcels, childhood disadvantage effect on surface area (SA) of each parcel (standardized beta value) is plotted against the principal functional gradient value of each parcel, with linear fit shown with a 95% confidence interval ($r = -0.37$ and $p_{spin} < .0001$). Warmer color indicates brain parcels that had greater surface area with higher childhood disadvantage, and cooler color indicates brain parcels that had smaller surface area with higher childhood disadvantage.

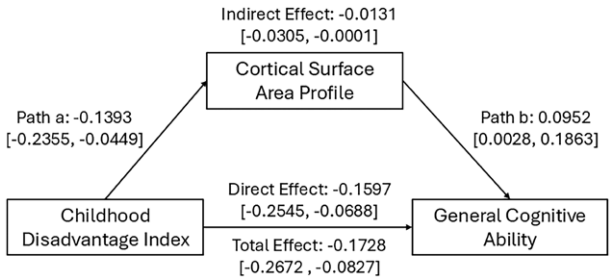

Figure 3. The mediation model. Standardized estimates of a and b paths, direct, indirect, and total effects are shown, along with the bootstrapped confidence intervals.

on GCA. Specifically, greater childhood disadvantage is associated with less similarity to an adult-like cortical organization of SA (i.e., unimodal–transmodal), which in turn relates to lower later-life GCA. Collectively, these findings suggest that childhood disadvantage may contribute to individual differences in later-life GCA partly by influencing cortical neuroanatomical development of SA during childhood and adolescence in a way that deviates from the normative cortical organizational principle.

Neurodevelopment including SA expansion is known to be nonuniform across the cortex and varies along the unimodal–transmodal axis of cortical organization (Hill et al., 2010; Sydnor et al., 2021). Childhood disadvantage has been shown to shape neurodevelopment by leading to faster maturation but a reduced window of plasticity during childhood and adolescence (Larsen et al., 2023; Tooley et al., 2021), which is particularly detrimental for higher-order association cortices that require a protracted period of development and maturation (Larsen et al., 2023; Sydnor et al., 2021; Tooley et al., 2021). Some of the putative mechanisms associated with childhood disadvantages such as malnutrition, stress, and low quality of education have all been suggested to affect cortical development and maturation (Blair & Raver, 2016). Our findings in late middle-aged and older men are consistent with these findings in youth by showing cortical regions that exhibited smaller SA with higher childhood disadvantage were exclusively in association cortices. Given prior work indicating fetal influences on cortical SA (Walhovd et al., 2024) and that cortical SA expansion reaches its plateau in adolescence (Bethlehem et al., 2022), the observed childhood disadvantage effects on later-life cortical SA of associative regions after controlling for age-related effects are likely reflective of disadvantage-linked maturational variabilities

that were established much earlier in life during the course of development.

Relatedly, we observed the differential expression of childhood disadvantage-cortical SA associations along the unimodal–transmodal axis of cortical organization implicated in cortical neurodevelopment. Specifically, higher childhood disadvantage tended to be associated with smaller cortical SA of transmodal regions related to higher-order mental functions, but with larger cortical SA of unimodal regions implicated in lower-order primary sensory and motor functions. This finding parallels a recent study in youth on environmental disadvantage (e.g., neighborhood poverty, crowding) and brain functional activity, which found higher disadvantage is related to lower activity in association cortices but higher activity in sensorimotor cortices (Sydnor et al., 2023). Likewise, another large-scale study examining the associations between childhood adversity and midlife cortical SA (i.e., age 45) found the effects to vary along the unimodal–transmodal axis, with the negative associations mostly clustered within transmodal regions (Gehred et al., 2021). These differential effects of childhood disadvantage on unimodal and transmodal regions (positive vs negative) reported in our study and others may be timing-dependent and relate to when the disadvantage occurs with respect to cortical development. For instance, stress, which relates to childhood disadvantage, is known to negatively affect the development and maturation of transmodal regions (e.g., prefrontal, default mode network; Kolk & Rakic, 2022; Rebello et al., 2018). Interestingly, stress is also known to accelerate the maturation of the cortical regions (Tooley et al., 2021). Because unimodal regions are developed earlier than transmodal regions, we speculate that stress that occurred during this period could accelerate their development, which might be overshot, resulting in the positive effect of childhood disadvantage on cortical SA. Together, our results provide novel evidence suggesting that the cortical embedding of childhood disadvantage can be observed even at a much older age in late midlife and older adulthood, which likely reflects disadvantage-linked effects on cortical SA that were established during critical periods of development, as the associations are organized in a way that mirrors both the spatiotemporal patterning of cortical development and the way disadvantage effects are expressed during childhood and adolescence.

We did not detect any significant childhood disadvantage effect on regional cortical SA in this older age cohort, but the small effect sizes are comparable to those of a prior large-scale study in middle-aged adults (N >1 000) that found significant associations between childhood adversity and cortical SA at the regional level (Gehred et al., 2021). Given that the effect size of the present study is small, future studies with larger sample sizes and more diverse samples are needed to replicate our findings. Nevertheless, the observed differential effects of childhood disadvantage on SA across the cortex underscores the importance of assessing the spatial patterning of subtle associations across the brain in addition to the magnitude of effect within individual regions (Vuoksimaa et al., 2016).

We further showed that there are cognitive consequences associated with childhood disadvantage effects on cortical SA. Individuals with higher childhood disadvantage had spatial SA profiles that were less closely aligned with the adult-like cortical hierarchical organization that spans from unimodal to transmodal cortices. These divergent spatial profiles can be interpreted as disadvantage-linked alterations of cortical neurodevelopment, thereby leading to GCA differences across the lifespan. Moreover, this reduced spatial alignment with the cortical hierarchical organization mediates 1.31% of the effects of childhood disadvantage on later-life GCA, a magnitude that is comparable to a study that detected 1.19% of childhood disadvantage effects on later-life general intelligence were mediated by total SA (Williams et al., 2023). However, later-life cortical SA spatial profile, but not total SA, was associated with childhood disadvantage in our study. The failure of replication could be due to differences in the operationalization of childhood disadvantage, as our study included socioeconomic and environmental risks, whereas the other study focused on psychological/environmental risks such as childhood abuse and related stressors. Although greater childhood disadvantage may tend to be associated with lower total SA, the differential effects we observed across unimodal and transmodal regions suggest that total SA may not be as robust or precise a measure as the cortical SA spatial profile. Regardless of these differences, later-life cortical SA appears to be a consistent neuroanatomical mediator of childhood disadvantage effects on later-life differences in GCA. It should be noted that this mediation is not necessarily exclusive to later-life GCA, as childhood disadvantage may have already started to affect early-life GCA through early-life cortical SA spatial profile. Although we were not able to examine this relationship due to the lack of early-life cortical SA data, future work in younger populations would be able to examine this hypothesis.

Finally, the modest amount of childhood disadvantage effects mediated by cortical SA profile and the remaining direct effects suggest that there must be other neural mediators. Based on studies that found modest effects mediated by gray matter macrostructural measures, it is possible that microstructural measures focusing on white matter could be promising mediators. For instance, the organization of brain structural connectome is implicated in cognitive function and is affected by childhood disadvantage (Kim et al., 2019; Tang et al., 2022). Additionally, more dynamic functional measures of brain connectivity and activity are likely to mediate childhood disadvantage effects on GCA. For instance, large-scale functional networks located within the association cortices are known to change in activity and connectivity, in response to complex cognitive demands (Menon & D'Esposito, 2022). Not surprisingly, childhood disadvantage also affects brain functional development along the unimodal–transmodal axis (Sydnor et al., 2023), suggesting that disadvantage-linked variations in functional networks could potentially lead to GCA differences. Taken together, future work focusing on measures of brain structural and functional connectomes as mediators of childhood disadvantage effects on later-life GCA is needed.

A few limitations are worth noting. First, our cohort included mostly white and non-Hispanic men, which means results may not generalize to women or other racial/ethnic groups, who may experience more disadvantages and other forms of disadvantage. Second, questions about childhood disadvantage were assessed retrospectively, which might be subject to recall bias. However, participants were largely twin pairs, and most of these reports were independently collected from two members of the same family, which partly mitigates the issue of recall bias. Third, we do not have measures of neighborhood disadvantages during childhood that are also known to shape cognitive and brain development and may

give rise to cognitive differences later in life. Fourth, other mediators such as later-life health status and adult SES may affect the CDI–GCA association, but are beyond the scope of this study. Future work on these putative mechanisms is needed. Lastly, the mediator does not temporally precede the dependent variable, which is a limitation in establishing causality. Future work examining cortical SA assessed at an earlier time than GCA is needed to confirm our findings.

Overall, childhood disadvantage effects on later-life GCA appear to be partly mediated, albeit to a small percent, by individual differences in the spatial profile of cortical SA, rather than total SA. This spatial profile is reflective of the extent to which an individual's cortical organization conforms to the overarching cortical organization principle that spans from unimodal to transmodal cortices. Our findings suggest that childhood disadvantage is associated with a divergence of the spatial profile from the cortical organization principle, which in turn is associated with lower GCA in late midlife and older adulthood. These results shed light onto the putative neuroanatomical mechanisms underlying how childhood disadvantage affects later-life GCA, which may inform policymaking and the development and improvement of intervention to mitigate the negative consequences on later-life brain and cognition.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

A.M. Dale is a founder and holds equity in CorTechs Laboratories, Inc. and also serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All other authors have nothing to disclose.

Data Availability

The Vietnam Era Twin Study of Aging data set and study materials are publicly available to qualified researchers, with restrictions. Information regarding data access can be found at https://psychiatry.ucsd.edu/research/programs-centers/vetsa/researchers.html. The study was not preregistered.

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