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Socioeconomic Position and Age-Related Disparities in Regional Cerebral Blood Flow Within the Prefrontal Cortex

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Abstract

Objective: Socioeconomic position (SEP) is associated with cerebrovascular health and brain function, particularly in prefrontal cortex and medial temporal lobe regions that exhibit plasticity across the life course. However, it is unknown whether SEP associates with resting cerebral blood flow (CBF), an indicator of baseline brain function, in these regions in midlife, and whether the association is (a) period specific, with independent associations for childhood and adulthood SEP, or driven by life course SEP, and (b) explained by a persistent disparity, widening disparity, or the leveling of disparities with age.

Methods: To address these questions, we analyzed cerebral perfusion derived by magnetic resonance imaging in a cross-sectional study of healthy adults ($N = 443$) who reported on childhood and adult SEP. Main effects were examined as an index of persistent disparity and age by SEP interactions as reflecting widening or leveling disparities.

Results: Stable high SEP across the lifespan was associated with higher global CBF and regional CBF (rCBF) in inferior frontal gyrus. However, childhood SEP was associated with rCBF in middle frontal gyrus, as moderated by age ($\beta = 0.04$, $p = .035$): rCBF was inversely associated with age only for those whose parents had a high school education or below. No associations were observed for the hippocampus or amygdala.

Conclusions: Life course SEP associations with rCBF in prefrontal cortex are suggestive of persistent disparities, whereas the age by childhood SEP interaction suggests that childhood disadvantage relates to a widening disparity, independent of global differences. These differential patterns in midlife may relate to disparities in later-life cerebrovascular and neurocognitive outcomes.

Keywords

cerebral blood flow; life course development; prefrontal cortex; socioeconomic position

INTRODUCTION

Socioeconomic position (SEP) reflects the material, social, and educational resources individuals can access, as well as their social status (1). SEP in childhood and adulthood is related to neurocognitive performance, from early in childhood through midlife and the aging process (2–6). In addition, SEP is an important predictor of health, including cerebrovascular health. Lower SEP in adulthood is associated with a higher incidence of stroke, whereas lower childhood SEP also relates to higher levels of stroke in part through its influence on adult SEP (7–9).

Neuroscience studies have begun to contribute to the understanding of the link between SEP and neurocognitive and physical health. This literature has focused on the role of the prefrontal cortex (PFC) and regions within the medial temporal lobe (MTL), such as the hippocampus and amygdala, given their sensitivity to environmental influences and their broad roles in cognition, emotion, and health (10–12). Among adults, low SEP has been correlated with structural differences in the hippocampus, amygdala, and PFC (13–15), as well functional differences in amygdala activity to emotional expressions (16,17) and PFC activity during effortful emotion regulation (18). These associations may be rooted in processes occurring in childhood and adolescence, because there is evidence that children and adolescents from lower SEP backgrounds exhibit smaller volumes of the hippocampus and PFC, with some mixed evidence concerning the amygdala (13,19–22). Additional evidence suggests an association between SEP and functional activation in PFC in children and adolescents (23,24). These studies, as well as others, reflect growing evidence that SEP is associated with the structure and function of PFC, as well as the hippocampus and amygdala.

Despite burgeoning interest in SEP and brain structure and function, few studies have examined the association between SEP and resting brain function. One study, for example, found that lower childhood income correlated with reduced connectivity of the default mode network in young adulthood (25), whereas another found that lower early childhood family income predicted reduced connectivity between both the amygdala and hippocampus and various cortical regions later in childhood (26). In addition, SEP-related differences in frontal electroencephalographic asymmetry at rest have been shown in adolescence (27). However, no studies have examined the association between SEP and any measure of resting brain function during midlife, nor have any studies examined SEP and resting cerebral blood flow (CBF) during any developmental stage or period of aging.

Resting, global CBF and regional CBF (rCBF) are important aspects of brain function that may plausibly be linked to SEP. CBF is a reliable indicator of baseline brain function (28), with a large proportion of the brain's energy use devoted to maintaining this baseline state (29). There is variation in the degree to which CBF is stable throughout midlife and aging. In particular, the amygdala and hippocampus have been shown to exhibit stability, whereas global CBF and rCBF in PFC decline throughout adulthood (30,31). rCBF may be considered as a general index of cerebrovascular health, particularly in relation to outcomes such as stroke (32). Moreover, it has been interpreted to reflect neural “preparedness” or expectation to act (33,34) and thus may play an important role in influencing cognitive,

emotional, and behavioral changes across the lifespan. Multiple mechanisms may link SEP and rCBF. Among the most plausible are those related to smoking and cardiometabolic risk, which are both linked to SEP (15) and have a physiologically plausible association with CBF (35). However, additional factors such as psychosocial stress and environmental experiences during development may also account for SEP-CBF associations (10–12,36).

The timing of exposure to different SEP levels is critical to understanding the SEP-rCBF association, because there may be associations specific to different developmental periods that are distinct from those of socioeconomic trajectories across the lifespan (14,37). From this theoretical perspective, SEP may be more influential at different developmental epochs. Early childhood, for example, may be a sensitive period in which early experiences may become “biologically embedded” and have long-lasting effects on brain function (37,38), with SEP in adulthood having little or independent influence. A second, complementary theoretical perspective highlights the importance of socioeconomic trajectories across the life course, reflecting either the stable accumulation of exposure to advantage or disadvantage, or the importance of upward or downward socioeconomic trajectories (14,37,39,40). Although not mutually exclusive, these patterns point to different possible underlying mechanisms driving the association between SEP and rCBF.

A second central question is whether SEP-related differences are persistent and stable across midlife or whether they may change with age. At least three different age-related patterns have been hypothesized in relation to socioeconomic health disparities (41–43): (1) age-as-leveler, in which the aging process eventually reduces the disparities between different SEP levels; (2) cumulative disadvantage, in which SEP-related disparities widen over time, either through the accumulation of exposures or steeper trajectories of age-related decline; and (3) persistent disparities, in which SEP-related differences in a given end point have their origin earlier in development and remain stable throughout midlife and aging. Given age-related decline in global CBF and rCBF in PFC during midlife (30,31), it is plausible that the age-as-leveler or cumulative disadvantage models may be the best fit for PFC, as SEP may be associated with the rate of normative decline. However, because the amygdala and hippocampus do not show change during this period, persistent associations seem most plausible, as in general there is stability.

The current study sought to examine the association between SEP and global CBF and rCBF in PFC and in the hippocampus and amygdala during midlife in a cross-sectional sample of healthy, community-based adults, to address gaps in the literature during this important period of lifespan aging. Given the direction of relations in previous studies of SEP and neurocognitive function, brain structure, and function, it was hypothesized that lower SEP would be associated with lower CBF. In addition, this study also sought to test (a) if period-specific or life course models best explained this association and (b) if SEP differences followed the cross-sectional pattern predicted by the persistent disparities model in hippocampus and amygdala, in which there would be an association that is not modified by age, and by the age-as-leveler or cumulative disadvantage models in PFC, in which the association between age and rCBF would differ by SEP level. Finally, we sought to examine whether patterns of association were independent of alternative explanatory factors or are specific to SEP.

MATERIALS AND METHODS

Participants

Participants were community-dwelling adults, aged 30 to 54 years, from the Adult Health and Behavior–Phase II (AHAB-II) study ($n = 490$, 52.1% female), a cross-sectional epidemiological registry of residents in Western Pennsylvania recruited by mass mailings and tested between February 2008 and October 2011. Eligibility was determined by interview, self-report, and clinical/laboratory assessment. Participants were ineligible based on the following: a history of cardiovascular disease or treatment; high blood pressure (resting systolic/diastolic blood pressure $\geq 160/100$ mm Hg); history of stroke or cerebrovascular disease; insulin-dependent diabetes or a fasting glucose of greater than 126 mg/dl; chronic hepatitis, renal failure, any neurological disorder, or lung disease requiring pharmacological treatment; alcohol consumption greater than five servings, 3 to 4 days per week; pregnancy or lactation; history of bipolar disorder or schizophrenia; and the use of any cardiovascular, psychotropic, glucocorticoid, lipid-lowering, or weight-loss medications. In addition, participants were excluded if they did not work at least 25 h/wk outside of the home or had shift work employment. All participants provided informed consent, and the study was approved by the University of Pittsburgh Institutional Review Board.

The current analysis includes 443 participants, with missing data due to the following: not completing or withdrawing from the perfusion neuroimaging protocol ($n = 35$); procedural magnetic resonance imaging difficulties or anatomical abnormalities ($n = 6$); language concerns ($n = 2$); and missing data on parental education in early childhood ($n = 4$). Sample characteristics are described in Table 1. Previous articles from this cohort employing CBF do not overlap with this analysis. These reports focused on total CBF and cardiovascular risks, the association between cognition and CBF, and the association between CBF and high-frequency heart rate variability (35,44,45).

Assessment of Socioeconomic Indicators and Life Course Disadvantage

The highest level of education achieved by either parent, as of the participant's early childhood, was used as an index of childhood SEP, whereas educational attainment was employed as an index of SEP in adulthood. Education was coded here as follows: 1 = high school graduate or less, including high school equivalency, 2 = 1 to 3 years of college, 3 = 4-year college graduate, and 4 = graduate degree completion. Parental education and participants' own educational attainment were moderately correlated ($r = .29$, $p < .001$). Education was chosen as an index of SEP to ensure that measures of childhood and adulthood SEP employed the same socioeconomic indicator, given that different measures of SEP may have different associations with health and brain outcomes (10,46).

To index life course SEP, childhood and adulthood SEP were combined into a single indicator (39,40). To create this indicator, low SEP was defined as below a 4-year college degree, whereas high SEP was defined as achievement of a college degree or higher. Consequently, the following four categories of life course exposure were created: (1) stable low SEP, with low parental education and educational attainment; (2) upward socioeconomic trajectory, indicated by low parental education and high educational achievement; (3)

downward socioeconomic trajectory, with high parental education followed by low educational achievement; and (4) stable high SEP, with high parental education and high educational achievement. Distributions of these categories are reported in Table 1.

Magnetic Resonance Image Acquisition

Magnetic resonance imaging scans were collected using a 3T Trio TIM whole-body scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. A pulsed arterial spin-labeling sequence was used to acquire resting perfusion images. Interleaved perfusion images, with and without arterial spin labeling, were obtained for a 5-minute 28-second period using gradient-echo echo-planar imaging. The pulsed arterial spin-labeling sequence employed a modified version of the flow-sensitive alternating inversion recovery method (47), applying a saturation pulse of 700 milliseconds after an inversion pulse. A 1000-millisecond delay separated the end of the labeling pulse and the time of image acquisition to reduce transit artifact. Acquisition parameters were the following: field of view = 240×240 mm, matrix = 64×64 , repetition time (TR) = 4000 milliseconds, echo time = 18 milliseconds, and flip angle = 90 degrees. Twenty-one slices (5-mm thick, 1-mm gap) were acquired sequentially in an inferior-to-superior direction, yielding 80 total perfusion images (40 labeled, 40 unlabeled, 2 initial discarded images allowing for magnetic equilibration); acquisition time for each slice was 45 milliseconds. Twenty-four seconds of equilibrium magnetization of brain (2 sets of 21 slices; TR = 8000 milliseconds; all other parameters as above) provided two images for CBF baseline quantification.

Neuroanatomical images were also acquired for both spatial co-registration of perfusion images and for use as morphological control variables. T1-weighted three-dimensional magnetization-prepared rapid gradient-echo images were acquired for 7 minutes 17 seconds using these parameters: field of view = 256×208 mm, matrix = 256×208 , TR = 2100 milliseconds, inversion time = 1100 milliseconds, TE = 3.31 milliseconds, and flip angle = 8 degrees (192 slices, 1-mm thick, no gap).

Image Processing and Analysis

Resting perfusion images were preprocessed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK). Neuroanatomical scans were segmented into grey and white matter tissue images. Perfusion images were realigned to the first image of the series, and a mean perfusion image was generated. The baseline images were realigned to the first of the perfusion images, and one averaged baseline image was then calculated from the two realigned images. Each individual's grey matter image was co-registered to the respective mean perfusion image. The 80 realigned perfusion images and one averaged baseline image were smoothed with a 12-mm full width at half-maximum isotropic Gaussian kernel. CBF imaging reconstruction began with pairwise subtraction (e.g., the even-numbered unlabeled/control image is subtracted from odd-numbered labeled image) of 40 labeled and 40 unlabeled perfusion images that were realigned and smoothed. Subtraction images were converted to an absolute CBF image series (48). A voxelwise CBF image and a global CBF value, in units of ml/100 g/min, were generated for each participant by averaging the perfusion CBF images. After image reconstruction, the co-registered grey matter image was warped to match the International Consortium for Brain Mapping 152

(Montreal Neurological Institute) grey matter template. The estimated warps (i.e., spatial normalization parameters) were then applied to the mean CBF and the grey matter images with voxel size of $3 \times 3 \times 3$ mm to preserve concentration of the image, using trilinear interpolation. A normalized mean CBF image was generated for each participant.

Mean rCBF values for a priori regions of interest were extracted using anatomically defined bilateral masks of the middle frontal gyrus (MFG), inferior frontal gyrus (IFG), amygdala, and hippocampus. Masks for each region of interest were defined by the Automated Anatomical Labeling system of the Wake-Forest University Pick-Atlas (49).

Assessment of Alternative Explanatory Factors

Cardiometabolic risk (reflecting waist circumference, resting systolic blood pressure, high-density lipoproteins, triglycerides, glucose, and total cholesterol), self-report of current smoking (yes/no), overall cognitive performance as estimated by the Weschsler Abbreviated Scale of Intelligence (50), and indices of measures of total gray matter, total cortical gray matter, and intracranial volume (ICV) derived from neuroanatomical scans were assessed to determine whether associations were attributable to alternative explanatory factors, as these variables have been associated with CBF in previous literature (28,30,35,51,52).

Methodological details are in Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A443>.

Data Analysis

Linear multiple regression was the primary analytic strategy and was implemented using SPSS 22.0 (IBM, Armonk NY). Analyses of SEP focused on two different approaches. First, to test competing theoretical models, we examined whether SEP in childhood and adulthood were associated with rCBF independently. In this set of models, parental education and educational attainment were entered into regression models simultaneously as predictors of rCBF. Second, we examined the association between life course SEP and rCBF, by employing dummy codes for the following trajectories: (1) stable low SEP, (2) an upward socioeconomic trajectory, and (3) a downward socioeconomic trajectory. The reference group for these analyses was those with stable high SEP.

To assess whether cross-sectional patterns best fit the persistent disparities, age-as-leveler, or cumulative disadvantage models, the main effects of period-specific or life course measures of SEP and their interaction with age were examined as predictors of global CBF and rCBF. If indicators of SEP were associated with rCBF or global CBF only as a main effect, this would be interpreted as consistent with persistent disparities. In contrast, a significant interaction between indices of SEP and age would be interpreted as consistent with the age-as-leveler or cumulative disadvantage model, depending on the nature of the interaction. Hence, this interaction would indicate that SEP was associated with different age-related patterns, potentially interpreted as cross-sectional estimates of age-related change, such that the disparity would either widen or narrow. When interactions were found, for SEP in particular, we conducted follow-up analyses with categorical indicators for each educational level (with a college degree as the reference group) and their interactions with age, to estimate the parameter for age at each individual level of SEP.

All analyses of rCBF employed global CBF as a covariate, so that all results are interpretable as “regional” after accounting for global differences.¹ Analyses controlled for racial/ethnic identification (categorical variable for white versus nonwhite self-reported racial/ethnic identity) (see Table 1 for detailed distributions), to ensure SEP-related associations are specific, as well as sex, which has been associated with CBF (53,54).

RESULTS

Age and Resting CBF

To test whether the association between socioeconomic disadvantage and CBF is modified by age, it was first necessary to examine the basic pattern of age-related variation across midlife. To do this, we employed a regression model using both age and age squared, to determine whether the pattern was linear or quadratic. Resting, global CBF declined in linear fashion with increasing age across midlife ($\beta = -0.11$, $p = .023$), with no evidence of quadratic change ($\beta = -0.01$, $p = .79$).

Similarly, there was no evidence of quadratic change in rCBF in IFG, MFG, hippocampus, or amygdala, irrespective of whether global CBF was included as a covariate (all $p \geq .27$). The linear term for age was significant and negative for IFG ($\beta = -0.18$, $p < .001$) and MFG ($\beta = -0.18$, $p < .001$), and it remained significant after controlling for global CBF (IFG: $\beta = -0.08$, $p < .001$; MFG: $\beta = -0.08$, $p < .001$), indicative of regional, linear decline with age that is not explained by age-related decrease in global CBF. However, there was evidence of stability in the MTL, because the unadjusted association with age was not significant for the hippocampus ($\beta = -0.05$, $p = .33$) or the amygdala ($\beta = -0.04$, $p = .42$). However, once accounting for global CBF, there was a regional, linear increase in CBF in the hippocampus ($\beta = 0.05$, $p = .014$) and amygdala ($\beta = 0.06$, $p = .040$).

Consequently, subsequent models incorporated the linear term for age, and its interactions with indices of disadvantage, and did not include a quadratic term.

Period-Specific Analyses: Separable Associations for Parent and Participant Education

For global CBF, analyses of the separate associations of parent and participant education are presented in Table 2. There were no significant relations between parental education or educational attainment and global CBF, either alone or in their interaction with age, with only a trend-level, positive association between parental education and global CBF ($\beta = 0.08$, $p = .068$).

In IFG, higher educational attainment was associated with greater rCBF ($\beta = 0.05$, $p = .018$), as reported in Table 2. There were no significant interactions with age nor main effects of parental education. This association was not explained by differences in cardiometabolic risk, cigarette smoking, ICV, total gray matter, total cortical gray matter, or performance on a

¹Robustness checks were conducted to determine whether the results were similar if rCBF was adjusted for global CBF before the regression model. To create these measures, we ran a regression model for rCBF in each region of interest with global CBF as a predictor and saved the unstandardized residual, to extract the unique variance in rCBF not explained by global CBF. Results were largely consistent with models employing global CBF as a covariate, indicating that the broad pattern of results is not dependent on the approach to adjustment for global CBF.

test of full-scale IQ (see Supplementary Table S1, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A443>), as the relation between participant education and rCBF in IFG remains significant after controlling for these variables.

In MFG, there was a significant interaction between age and parental education ($\beta = 0.04$, $p = .035$), with no other main effects or interactions for indices of SEP (Table 2). This interaction indicates that age-related differences in rCBF, estimated from cross-sectional data, differ depending on parental education level. This association remains significant and consistent in direction after controlling for cardiometabolic risk, cigarette smoking, intracranial volume, total gray matter, total cortical gray matter, or performance on a test of full scale IQ (see Supplementary Table S1, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A443>). To understand this interaction more clearly, we conducted a follow-up analysis using categorical indicators of parent and participant education, with college education as the reference group. In this analysis, the interaction between age and a high school degree or less was significant ($\beta = -0.06$, $p = .026$), whereas the interactions between age and some college ($\beta = -0.01$, $p = .64$) and a graduate degree ($\beta = -0.001$, $p = .97$) were not. As illustrated in Figure 1, this indicates that the interaction between age and parental education is driven by the presence of a steeper decrease with age for those adults whose parents did not have more than a high school degree, compared with very little age-related difference for all other groups.

There were no significant associations between parental or participant education, as main effects or in their interaction with age, and rCBF in the hippocampus or the amygdala (Table 2).

Life Course Exposure to Disadvantage

Compared with those of stable high SEP across childhood and adulthood, stable low SEP associated with lower global CBF at rest ($\beta = -0.11$, $p = .03$). As noted in Table 3, there were no significant interactions between age and indices of life course SEP.

As depicted in Table 3, stable high SEP was associated with higher rCBF in IFG. In particular, stable low SEP ($\beta = -0.05$, $p = .026$), upward ($\beta = -0.04$, $p = .045$), and downward ($\beta = -0.06$, $p = .002$) socioeconomic trajectories were associated with decreased rCBF in IFG. There were no interactions between indicators of life course SEP and age (all $p \geq .27$). In addition, these associations remain significant, and in the same direction, when controlling for cardiometabolic risk, cigarette smoking, ICV, total gray matter, total cortical gray matter, or full-scale IQ (see Supplementary Table S2, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A443>).

Similarly, in MFG life course SEP was associated with differences in rCBF that were not modified by age (Table 3). In particular, downward ($\beta = -0.05$, $p = .008$) socioeconomic trajectories were associated with decreased rCBF in MFG compared with stable high SEP, whereas there were no interactions between indices of life course SEP and age (all $p \geq .12$). When controlling for cardiometabolic risk, cigarette smoking, ICV, total gray matter, total cortical gray matter, or full-scale IQ, these associations remained significant (see

Supplementary Table S2, Supplemental Digital Content 1, <http://links.lww.com/PSYMED/A443>).

Consistent with period-specific analyses, there were no significant associations between patterns of life course SEP, as main effects or in their interaction with age, and rCBF in the hippocampus or the amygdala (Table 3).

DISCUSSION

This study is the first to demonstrate that SEP is associated with differences in rCBF at rest, a basic indicator of baseline brain function (28). In general, lower SEP was associated with lower rCBF. Notably, however, this association was independent of global CBF and regionally specific to the PFC, compared with MTL regions, whether examining period-specific or life course measures of SEP. In addition, these associations were independent of brain morphology, ICV, and overall cognitive performance. Despite some previous reports of SEP-related differences in structure and function of the hippocampus and amygdala (13–15,55,56), no differences in rCBF were observed in the hippocampus and amygdala, even in this large sample of adults at midlife.

There is evidence that both period-specific indices of SEP as well as life course exposures are associated with rCBF, providing support for complementary theoretical perspectives (14,37,38,40,41). With respect to age-related differences, associations between rCBF and life course and adult SEP were not modified by age, whereas the association between rCBF and childhood disadvantage was modified by age. For life course exposure, high SEP across the life course was associated with higher global CBF and higher rCBF in IFG, whereas a downward trajectory in SEP predicted lower rCBF in MFG. Moreover, these differences were stable—SEP was not a moderator of age, and thus patterns of association with life course SEP was consistent with a model of persistent disparities in both regions of the PFC. Adult SEP followed a similar pattern, as higher SEP in adulthood correlated with greater rCBF in IFG but not MFG, with no age differences by SEP level, evidence that is consistent with a persistent disparity. Consequently, and in speculation, most SEP-related disparities in midlife may emerge before the age of 30 years and remain consistent across the subsequent decades. Nevertheless, childhood SEP exhibited a different pattern. Lower childhood SEP and particularly having parents with no more than a high school degree were associated with significant age-related differences, consistent with steeper age-related decline estimated from cross-sectional data, compared with relatively little age-related difference for higher levels of parental education. This agrees not only with a period-specific model but also with a model of cumulative disadvantage in which disparities widen across time, perhaps indicative of the earlier onset of the cerebral aging process. It also suggests that growing up in a family where parents have higher education levels may buffer against age-related declines in rCBF in MFG.

SEP-related differences in resting brain function may have significant consequences for disparities in cerebrovascular health, cognition, and emotion during the aging process. In this large neuroimaging sample, the effects observed for SEP are small to moderate in magnitude and, because this was a healthy sample, there is no evidence that rCBF

differences of this magnitude are currently associated with such functional disparities. However, as resting brain function has been interpreted to reflect neural “preparedness” or expectation to act (33,34), it may exert more subtle effects than such measures are sensitive to in midlife and may play an increasingly important role influencing cognitive, emotional, and behavioral changes and SEP-related disparities across the aging process. This may be particularly true if such differences are more likely after lower rCBF surpasses a “threshold” under which deficits begin to emerge, as has been hypothesized in so-called “reserve” models of cognitive aging (57). In addition, rCBF may be interpreted as a general index of cerebrovascular health. Cerebrovascular disease and outcomes, such as stroke, are often diseases related to acute, low CBF in critical regions. Although there is limited evidence of the prospective prediction of stroke by rCBF, lower rCBF may provide a smaller buffer to the potentially adverse consequences of acute decreases in rCBF (32). Consequently, SEP disparities in rCBF may contribute to the disparities observed in cerebrovascular disease.

The regional dissociation between PFC and hippocampus and amygdala was unexpected and sheds light on possible mechanisms underlying the SEP-rCBF association in PFC. Amygdala and hippocampal structure and function have been associated with SEP and differences in stress and emotion that are thought to contribute to SEP-related disparities in outcomes (10,11,13), although work in this area is not uniform, with several studies of midlife samples finding no SEP associations with medial temporal regions. The fact that differences with rCBF are only observed in PFC suggests that differences in aging processes as well as vasculature may be of importance. PFC and MTL regions exhibited different patterns of age-related association in this cross-sectional sample. Consistent with the previous literature (30), PFC regions exhibited less rCBF with increasing age whereas MTL regions did not exhibit an association with age, when global CBF was not controlled. When global CBF was accounted for rCBF in PFC continued to exhibit an inverse association with age while MTL exhibited a positive association with age. Consequently, the regional dissociation may indicate that mechanisms are either similar to those that account for CBF decline or primarily influence regions that are already susceptible to age-related decline. In addition, IFG and MFG are primarily served by distal branches of the middle cerebral artery, closer to watershed areas in cortex, whereas the hippocampus and amygdala are served by less distal branches of the posterior cerebral artery (58). It is possible that the distal arterial branches are more susceptible to differences in cardiometabolic risk that are typically associated with SEP. In the current study, there was no evidence that cardiometabolic risk or smoking behavior accounted for any of these differences. However, this measure is a cross-sectional snapshot of current cardiometabolic risk and does not necessarily capture all subtle variations in risk nor the degree to which cardiometabolic risk has been elevated at specific epochs or cumulatively across the life course. Consequently, cardiometabolic differences early in the life course may explain the disparities that are observed here. In addition, indicators of brain morphology and blood flow are not interchangeable, and it is possible for such indicators to show dissociable patterns of association with other factors, such as SEP.

Hypothesized mechanisms underlying the present patterns of results must also address the age-related pattern of disparities for global and regional differences observed, as well as the patterns across PFC regions. As noted earlier, findings predominantly supported a model of persistent disparities, suggesting that they emerge before midlife, and thus, any possible

causal mechanisms must be operating before midlife as well. Similarly, the specific association of childhood SEP with age-related differences in MFG could reflect an early life determinant of the brain aging process. Such timing implicates a range of possible causal mechanisms earlier than midlife, including experiences in childhood and adolescence. There are a number potential mechanisms, including stress, nutrition, toxin exposure, and early differences in health and health behavior (11,12,15). Moreover, developmental experiences of threat and deprivation, including those related to maltreatment, violence exposure, and environmental enrichment, may account for the observed differences (36). In addition, the association between downward SEP trajectories and rCBF in MFG might be particularly associated with mechanisms related to socioeconomic instability or shocks, which suggests that stress-related mechanisms may be particularly important. In IFG, the combination of a positive relation between educational attainment and rCBF as well as high, stable SEP compared suggests that this experience of high SEP across the life course is the driving factor for this association. Consequently, plausible associated mechanisms are most likely to be those that are consistent, stable, and able to exert extended influence. In addition to the mechanisms noted earlier, this raises the possibility that the language environment and language experience are important. IFG has been particularly implicated in language function (59,60), and it may be the combination of a strong language environment, with parental education as a proxy, and both the practice, environment, and skill indicated by educational attainment that has a proximal influence on IFG, as compared with MFG. Future research with longitudinal life course data and rich assessments of potential exposures and mediators is necessary to address these questions.

A number of methodological challenges limit the extent of the conclusions that can be drawn from this study. First, the cross-sectional nature of the data precludes causal inferences. It may be that rCBF and SEP are associated because of the effect of rCBF on SEP or because of a third variable, rather than the effect of SEP on rCBF. However, given that brain structure, IQ measures, and cardiometabolic risk do not account for this covariance, a third variable is less likely but cannot be ruled out. Moreover, reverse causation is less likely for childhood SEP, unless current rCBF may influence recall of childhood SEP levels. Second, estimates of childhood SEP and life course SEP are limited based on retrospective reports, and life course SEP exposures are thus inferred from data about two periods collected at a single time point. In addition to possible recall bias, this may underestimate the true variability in patterns of life course SEP. Third, age-related differences in rCBF are employed in cross-sectional data, and thus, any potential inferences regarding change or aging are limited as they are estimated from cross-sectional age differences in a single cohort, rather than from measuring age-related change within individuals longitudinally. Consequently, it is possible that cohort differences rather than differences in age-related change contribute to age differences in this sample, particularly the inverse association between age and rCBF in MFG observed only for those whose parents had a high school education or below. As older participants likely had parents born decades earlier when the prevalence of higher education was lower, the meaning of educational level for social prestige may differ across the age range for this sample, potentially contributing to this finding. Fourth, it cannot be concluded that only PFC is associated with SEP. Additional brain areas, for which there were no a priori hypotheses, may also exhibit rCBF differences

associated with CBF that are independent of global CBF. Finally, it will be important to replicate and confirm findings in additional samples, especially as the magnitude of effects is small to moderate and it will be important to determine whether they are robust.

A second set of limitations involves that nature of the sample and the ranges and meaning of SEP measures. First, although the size of this neuroimaging sample is a significant strength of the study that allowed examination of effects of small to moderate magnitude, the sample is not representative of all adults in this age range. In particular, because the sample is selected to be healthy and at least employed part time, it is likely that this sample is missing the full range of variation in SEP and does not include those of extremely low SEP or adults who are already exhibiting early onset, chronic health problems. In addition, it is possible that the meaning of education level has changed across historical cohorts. Accordingly, inferences are limited by the inability to separate life course measures distinctly from historical cohort.

Despite these limitations, there is an association between SEP and rCBF that is independent of global CBF and specific to the PFC, as compared with the hippocampus and amygdala, that is indicative of the importance of particular developmental epochs as well as life course SEP. Although the differences related to life course and adult SEP seem persistent across midlife, there is also evidence that childhood SEP is associated with different age-related patterns across midlife, which suggests that disparities widen as early advantage may buffer against more typically expected decreases in rCBF. Consequently, SEP is associated with differences in cerebrovascular function in midlife that may confer greater risk for cerebrovascular problems as well as changes in brain substrates for cognitive, affective, and behavioral processes in the aging process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

CBF	cerebral blood flow
IFG	inferior frontal gyrus
MFG	middle frontal gyrus
MTL	medial temporal lobe
PFC	prefrontal cortex

rCBF	regional cerebral blood flow
SEP	socioeconomic position
TR	repetition time

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FIGURE 1.

Age and rCBF in MFG, by level of parental education. Trajectories come from analyses with categorical dummy codes for different levels of parental education and educational achievement and their interaction with age to estimate the association between age and rCBF for each level of education. College education was the reference group for all.

Unstandardized coefficients and standard errors for age and its interaction with parental education levels are as follows: age: $B = 0.03$, $SD = 0.05$; age by graduate degree: $B = -0.002$, $SD = .07$; age by some college: $B = -0.04$, $SD = 0.08$; and age by high school degree or less: $B = -0.13$, $SD = 0.06$. Color image is available only in online version (www.psychosomaticmedicine.org).

TABLE 1.

Sample Characteristics

Characteristic	<i>n</i> (%) or <i>M</i> (<i>SD</i>)
Age, y	42.5 (7.3)
Sex, female	231 (52.1)
Parental education	
High school or below	182 (41.1)
Some college	61 (13.8)
College graduate (Bachelors)	115 (26.0)
Graduate degree	85 (19.2)
Educational attainment	
High school or below	40 (9.0)
Some college	77 (17.4)
College graduate (Bachelors)	174 (39.3)
Graduate degree	152 (34.3)
Life course exposure	
Stable low SEP	87 (19.6)
Upward	156 (35.2)
Downward	30 (6.8)
Stable high SEP	170 (38.4)
Racial/ethnic identity	
White	371 (83.7)
African American	62 (14.0)
Asian American	6 (1.4)
Native American	2 (0.5)
Multiracial	2 (0.5)
Employment status: full-time	396 (89.4)
Own home	341 (77)
Own working motor vehicle	419 (94.6)
Family income (dollars)	76,817 (43,969)
Household size (residents)	2.7 (1.4)
Marital status	
Married/living with partner	280 (63.2)
Single	100 (22.6)
Widowed	2 (0.5)
Divorced/separated	61 (13.8)
Current smoker	
Yes	67 (15.2)
No	374 (84.8)
Metabolic risk	
Waist circumference, in	90.4 (14.0)
Systolic blood pressure, mm Hg	115.0 (11.2)

Characteristic	<i>n</i> (%) or <i>M</i> (SD)
Triglycerides, mg/dl	109.8 (68.7)
Total cholesterol, mg/dl	199.3 (38.1)
HDL, mg/dl	55.4 (14.8)
Glucose, mg/dl	98.3 (11.1)
Full-scale IQ	113.3 (12.4)
CBF, ml/100 g/min	
Global	57.9 (10.4)
IFG	50.5 (9.2)
MFG	52.3 (10.2)
Amygdala	51.5 (10.3)
Hippocampus	48.5 (8.9)

SEP = socioeconomic position; CBF = cerebral blood flow; IFG inferior frontal gyrus; MFG = middle frontal gyrus; HDL = high-density lipoprotein.

TABLE 2.

Separable Associations Between Parental and Participant Education and CBF

	Global		MFG		IFG		Hippocampus		Amygdala	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Global CBF	—	—	0.97	<.001	0.96	<.001	0.90	<.001	0.86	<.001
Age	−0.17	<.001	−0.05	.005	−0.05	.01	0.05	.019	0.06	.020
Sex (female = 1)	0.45	<.001	−0.12	<.001	−0.13	<.001	0.01	.85	−0.02	.54
Race (white = 1)	−0.02	.62	0.01	.62	−0.03	.19	−0.03	.19	−0.02	.39
Parental education	0.08	.068	0.002	.92	0.01	.74	0.00	.99	−0.01	.72
Participant education	0.01	.80	0.01	.43	0.05	.018	−0.02	.39	0.02	.40
Age by parental education	0.04	.38	0.04	.035	0.03	.14	−0.02	.50	0.01	.73
Age by participant education	−0.02	.65	−0.02	.16	−0.01	.66	0.02	.29	0.01	.69

MFG = middle frontal gyrus; IFG inferior frontal gyrus; CBF = cerebral blood flow.

TABLE 3.

Life Course SEP and CBF

	Global		MFG		IFG		Hippocampus		Amygdala	
	β	p	β	p	β	p	β	p	β	p
Global CBF	—	—	0.98	<.001	0.96	<.001	0.90	<.001	0.86	<.001
Age	−0.10	.14	−0.02	.48	−0.02	.44	0.06	.065	0.08	.040
Sex (female = 1)	0.45	<.001	−0.12	<.001	−0.12	<.001	0.004	.87	−0.02	.56
Race (white = 1)	−0.02	.67	0.00	.99	−0.03	.10	−0.02	.34	−0.02	.53
Stable low SEP	−0.11	.030	−0.01	.45	−0.05	.026	0.02	.40	−0.02	.43
Downward	−0.01	.88	−0.05	.008	−0.06	.002	0.04	.098	0.01	.67
Upward	−0.09	.069	−0.03	.078	−0.04	.045	0.02	.54	0.02	.55
Age by stable low SEP	−0.01	.83	−0.03	.12	−0.02	.27	−0.01	.82	−0.01	.78
Age by downward	−0.05	.26	0.01	.45	0.003	.87	−0.04	.12	−0.03	.25
Age by upward	−0.08	.18	−0.03	.19	−0.02	.33	0.004	.88	−0.01	.77

MFG = middle frontal gyrus; IFG inferior frontal gyrus; CBF = cerebral blood flow; SEP = socioeconomic position.

Stable high SEP is the reference group in all models, and thus, no parameters for this group are estimated.