Perceived Stress and Change in Cognitive Function Among Adults 65 Years and Older

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Objective: Exposure to acute and chronic stress can affect learning and memory, but most evidence comes from animal studies or clinical observations. Almost no population-based studies have investigated the relation of stress to cognition or changes in cognition over time. We examined whether higher levels of perceived stress were associated with accelerated decline in cognitive function in older blacks and whites from a community-based population sample. **Methods:** Participants included 6207 black and white adults (65.7% black, 63.3% women) from the Chicago Health and Aging Project. Two to five in-home assessments were completed over an average of 6.8 years of follow-up and included sociodemographics, health behaviors, psychosocial measures, cognitive function tests, and health history. Perceived stress was measured by a six-item scale, and a composite measure of four tests of cognition was used to determine cognitive function at each assessment. **Results:** Mixed-effects regression models showed that increasing levels of perceived stress were related to lower initial cognitive scores ($B = -0.0379$, standard error = 0.0025, $p < .001$) and a faster rate of cognitive decline (stress × time interaction: $B = -0.0015$, standard error = 0.0004, $p < .001$). Results were similar after adjusting for demographic variables, smoking, systolic blood pressure, body mass index, chronic medical conditions, and psychosocial factors and did not vary by race, sex, age, or education. **Conclusions:** Increasing levels of stress are independently associated with accelerated declines in cognitive function in black and white adults 65 years and older. **Key words:** aging, cognitive function, longitudinal, risk factors, stress.

BMI = body mass index; **CHAP** = Chicago Health and Aging Project; **MMSE** = Mini Mental State Examination; **PSS** = Perceived Stress Scale; **SBP** = systolic blood pressure.

INTRODUCTION

Previous research shows that exposure to acute and chronic stress can affect learning and memory function, but much of the evidence for this relation comes from clinical observations or basic neuroscience studies (1). More recent evidence derives from experimental studies with humans (2–4), yet there are almost no population-based studies with longitudinal data on cognitive function that have examined the impact of stress on cognition. Evidence from both animal and human studies is suggestive, however. Animal studies have shown that psychological stress can lead to cellular changes in regions of the hippocampus, decreased proliferation of neurons in the dentate gyrus, and loss of hippocampal volume resulting in atrophy and cognitive deficits (5–7). In humans, early life stress (e.g., childhood adversity or trauma exposure) has been associated with enduring neuropsychiatric effects such as depression (8) and long-term deficits in cognitive function (9). Among adults exposed to trauma, those who develop posttraumatic stress disorder are at greater risk for cognitive impairment compared with those who do not develop posttraumatic stress disorder (10). We know that chronic stress in adults is associated with hormonal and inflammatory indicators of accelerated aging (11) as well as excess risk of cardiovascular disease morbidity and mortality, including increased stroke risk (12,13). We recently reported that greater stress levels were related to increased odds of magnetic resonance imaging–defined infarcts in addition to lower total brain volumes (14). Several other studies have shown that various types of stressful exposures in childhood and adulthood are associated with lower regional volumes in the brain (e.g., hippocampus; amygdala) in adults (15–18). Finally, stress has been linked with a number of risk factors, for example, hypertension and smoking, known to affect cognitive functioning (19).

Taken together, these lines of evidence suggest that chronic stress may be related to poorer cognitive performance and worse memory function in older adults and declines in cognitive function over time. We tested these hypotheses in a community-dwelling sample of more than 6200 adults 65 years and older, with nearly 7 years of follow-up. We also examined whether selected chronic medical conditions, health behaviors, vascular risk factors, or other psychosocial factors related to stress or cognitive function could explain or modify the relation of perceived stress to cognitive function.

METHODS

Study Design and Procedures

Participants were from the Chicago Health and Aging Project (CHAP), a longitudinal population study of common chronic health problems among adults 65 years and older. CHAP study design and population characteristics have been published (20,21). Briefly, a complete census of three adjacent community areas in south Chicago, IL, was completed between 1993 and 1997, and all residents identified 65 years or older were invited to participate; 6158 (78.9% of eligible) persons agreed. This is the CHAP Original Cohort. The study population reflects the race/ethnicity makeup of the community areas at the time of the census, predominantly black and non-Hispanic white (<1% reported another race category or Hispanic ethnicity). Both black and white residents for these community areas are from a broad range of socioeconomic backgrounds (20). Six data collection cycles have been completed. All cycles included in-home interviews with structured questions on sociodemographics, psychosocial variables, medical history, and physical and cognitive performance tests, with data obtained every 3 years, on average: 1993 to 1997 (cycle 1), 1997 to 1999 (cycle 2), 2000 to 2002 (cycle 3), 2003 to 2005 (cycle 4), 2006 to 2008 (cycle 5), and 2009 to 2011 (cycle 6).

Beginning with data collection cycle 3, residents from the CHAP community areas who had since turned 65 years old and who were identified through

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the previous community census or commercially available lists were invited to participate in CHAP. As cycle 2 was ending, a community census of a fourth adjacent community area was taken, so beginning with data collection cycle 4 (i.e., in 2003), age-eligible persons from this fourth adjacent community area also were invited to participate. These are the CHAP Successive Cohorts, and they follow the same 3-year interview cycles and complete the same measures as the CHAP Original Cohort. For the present analyses, persons with valid data on perceived stress, which was completed at cycle 2 for Original Cohort participants and during the initial interview cycle for Successive Cohort participants (i.e., cycle 3, 4, or 5, depending on when they joined CHAP), and at least 2 assessments (range, 2–5; >65% had ≥3) of cognitive function were eligible for inclusion. Thus, our sample included 6207 adults (63.3% women; 65.7% black, 34.3% non-Hispanic white), 3012 from the Original Cohort, and 3195 from the Successive Cohorts. Signed informed consent forms were obtained from each participant, and the institutional review board of Rush University Medical Center approved the study.

MEASURES

Perceived Stress

Perceived stress was measured by six items from the Perceived Stress Scale (PSS), which assesses the degree to which a respondent evaluates situations that occurred in the previous month as stressful; prior research characterizes the PSS as and an indicator of global stress experienced by a person (22,23). The PSS administered as part of the CHAP in-home interview was shortened from 10 to 6 items given concerns about overall participant burden owing to the wide range of assessments completed as part of the CHAP in-home interview. These six items, shown in Box 1, correlate more than 0.95 with a published four-item version of the PSS (23). Response options for each item ranged from never (0) to often (3); after reverse-coding positively worded items, responses to all items were summed (range, 0–18) to create an overall score, with higher scores indicating greater stress. The PSS is well validated and has been used widely in epidemiologic studies (22,23). The six PSS items show good reliability (Cronbach coefficient $\alpha = .75$) in CHAP and have been previously associated with magnetic resonance imaging indicators of subclinical cerebrovascular disease within CHAP (14).

BOX 1. Six Items From the Perceived Stress Scale Used In Chicago Health and Aging Project

1. In the last month, how often have you been upset because of something that happened unexpectedly?
2. In the last month, how often have you felt that you were unable to control the important things in your life?
3. In the last month, how often have you felt that confident about your ability to handle your personal problems?
4. In the last month, how often have you felt that things weren't going your way?
5. In the last month, how often have you felt that you were on top of things?
6. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Item responses ranged from never (0) to often (3). Scores for positively worded items were reverse coded, and responses to all items were summed (range, 0–18) to create an overall score, where higher scores indicate greater stress.

Cognitive Function

At each cycle of data collection, four brief tests of cognitive function were administered, including the oral version of the Symbol Digit Modalities test (24), a test of perceptual speed in which participants are asked to identify as many digit-symbol matches as possible in 90 seconds; the immediate and delayed recall of 12 ideas contained in the East Boston Story (25), both of which measure episodic memory; and the Mini Mental State Examination (MMSE) (26). The MMSE measures global cognition and is commonly used as a screening tool for cognitive impairment. As previously reported (27,28), a composite of all four tests was created by converting the raw scores on each test to *z* scores, using the mean and standard deviation (SD) from the initial assessment in the population, and then averaging the *z* scores, with higher scores indicating better cognitive function. The composite cognitive score was used in our primary analyses.

Covariates

Age was assessed by self-reported date of birth and modeled continuously, centered at age 75 years. Race was self-identified based on 1990 census categories. More than 98% of respondents in the CHAP neighborhoods were African American or non-Hispanic white; therefore, race was coded as black versus non-black (referent). Other covariates were sex, self-reported years of education completed (modeled continuously and centered at 12 years), and several risk factors or indices of health and disease. Systolic blood pressure (SBP) was measured manually and considered the average of three measures of systolic pressure (two while sitting and one after standing 1 minute); SBP was modeled continuously, centered at 135 mm Hg. Height and weight were measured with standard protocols and used to calculate body mass index (BMI; in kilograms per meter squared); BMI was modeled continuously, centered at 28. Smoking status was obtained based on self-report and modeled categorically as current, former, or never smoker (referent). Prevalent chronic conditions were assessed by several questions asked during the CHAP in-home interview, including history of heart disease, stroke, diabetes, cancer, hypertension, and hip fracture. The number of chronic medical conditions present at the initial interview when stress was measured was deemed an indicator of chronic illness and modeled continuously (29). Use of antihypertensive medications was modeled as a yes/no variable and based on self-report and confirmed by medication review at the time of the in-home interview.

In addition, several measures of psychosocial functioning, obtained at the cycle 2 data collection or when perceived stress was measured, were included in secondary analyses. Depressive symptoms were measured with a 10-item version of the Center for Epidemiologic Studies Depression Scale, specifically developed for use with older cohorts (30). Participants respond yes or no to each item, reporting whether they had experienced that symptom during the past week; a summary score (range, 0–10) was created and modeled continuously. Neuroticism was assessed by four items from the Neuroticism scale of the NEO Five Factor Inventory (31). Consistent with prior work (32), scores on the four items were summed and then

multiplied by 3 to make the score comparable with the original 12-item version of the scale. Participation in cognitively stimulating activities was quantified with an established scale (33) in which participants rated frequency of participation in the past year in each of seven cognitive activities (e.g., playing card games, reading a newspaper, and listening to the radio) on a 5-point scale. Social engagement was measured by four questions about participation in social and productive activities and summed across items for a total social engagement score (34). Social network size was quantified by standard questions asking the number of friends and family members seen at least once per month (34).

Data Analysis

Mixed-effects regression models (35) tested the association of perceived stress with initial level of cognitive function and rate of cognitive decline. These models offer several advantages to analyzing repeated-measures data, including the following: a) initial level of function and rate of change are modeled as sources of random variability; b) the same number of observations are not required across participants; and c) the time between observations is not assumed to be constant across persons or testing occasions (36). Random intercepts and random slopes were included in all models. Using data from up to five cycles of data collection (initial interview when perceived stress was measured and up to four follow-up cycles), we first ran an unadjusted model (Model 1), which included perceived stress at baseline, time (modeled as a continuous variable in years, months, and days since the initial interview), and the perceived stress × time interaction. Then, on the basis of prior analyses of cognitive decline within the CHAP cohort (27,33), we included the following terms in Model 2: age, sex, education, race, and interactions terms of age × time, education squared (to account for the known quadratic relation of educational attainment with cognitive decline in the CHAP cohort (28)) age × sex, age × education, and race × education. Subsequently, a risk factor–adjusted model (Model 3) was estimated in which terms for SBP, BMI, and BMI-squared (to account for previously observed nonlinear associations of BMI with cognitive decline in the CHAP cohort (29)), smoking status, prevalent chronic conditions, and use of antihypertensive medications were added. This was followed by another risk factor–adjusted model (Model 4) that further adjusted for depressive symptoms, neuroticism, social engagement social networks, and cognitively stimulating activities.

Because little is known about whether the effects of perceived stress on cognitive outcomes vary by demographic characteristics, we conducted additional models to test whether stress interacted with race, sex, age, or education to influence cognitive functioning. The stress × race, stress × sex, and stress × education interactions were nonsignificant ($p > .10$); however, the stress × age interaction was significant ($B = -0.0011$, standard error [SE] = 0.0003, $p < .001$). Subsequently, we evaluated a three-way stress × age × time interaction to determine if the effect of stress on cognitive decline varied as a function of age, but there was no evidence for this ($B = -0.0001$, SE = 0.0001, $p = .21$). Thus, none of these interactions are further reported in the article. Finally, to assess the stability of our global cognitive measure, we conducted sensitivity analyses, repeating the models described above and substituting the individual cognitive measures (modeled as individual z scores in separate analyses) for the global cognitive measure.

Model assumptions about linearity, normality, independence, and homoscedasticity of errors were assessed graphically and analytically and were adequately met. Analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Our analytic sample included 6207 persons with valid data on the PSS and a minimum of two assessments of cognitive function over an average (SD) of 6.8 (3.2) years of follow-up, although 65% completed more than two cognitive assessments (35% completed two, 32.6% completed three, 20.4% completed four, and 12% had five cognitive assessments). The mean (SD) global cognitive function score at the initial assessment was 0.31 (0.67; range, −3.02 to 1.73); average annual decline was 0.048 units ($p < .001$). Correlations (r) among the individual cognitive tests ranged from 0.48 (East Boston Story immediate recall with Symbol Digit Modalities test) to 0.66 (East Boston Story delayed recall with MMSE). The mean (SD) PSS score in our sample was 5.22 (3.30). Blacks reported higher levels of stress than did whites (mean [SD] = 5.57 [3.29] versus 4.56 [3.22]; $t = 11.5$, $p < .001$), and men reported lower levels than did women (mean [SD] =4.98 [3.13] versus 5.36 [3.39]; $t = 4.4$, $p < .001$). Perceived stress was inversely correlated with education ($r = -0.17$, $p < .001$) but unrelated to age ($r = 0.017$, $p = .55$). Mean (SD) or n (%) for all covariates, perceived stress, and cognitive function are shown in Table 1.

Results of the mixed-effects regression models assessing the relation of perceived stress with overall cognitive function are shown in Table 2. A significant main effect of perceived stress was observed. In the initial unadjusted model (Model 1), each 1-point higher stress score was associated with a 0.0379-unit lower initial global cognitive score ($p < .001$). Moreover, perceived stress was associated with an increased rate of cognitive decline as shown by the significant stress × time interaction term. For each 1-point higher stress score, cognitive function declined by 0.0015 units per year ($p < .001$). Thus, a person with a high stress score initially (score = 10, 90th percentile) would have a predicted annual decline in cognitive function of 0.0552 units compared with a person with a low level of stress (score = 1, 10th percentile) whose annual cognitive decline would be estimated as 0.0417 units. In subsequent models, both the main effect of stress on initial level of cognitive function and the per-year change in cognitive function related to stress remained after controlling for demographic characteristics and their interactions (Model 2) as well as the potentially confounding effects of SBP, BMI, smoking, prevalent chronic conditions, and use of antihypertensive medication (Model 3). Further adjustment for depressive symptoms, neuroticism, social engagement, social network size, and cognitively stimulating activities diminished the main effect of stress on initial level of cognition,

TABLE 1. Participant Characteristics: Chicago Health and Aging Project

Age, M (SD), y	72.9 (6.23)
Sex, *n* (%)	
Women	3,927 (63.3)
Men	2,280 (36.7)
Race/Ethnicity, *n* (%)	
Black	4,081 (65.7)
Non-Hispanic white	2,126 (34.3)
Education, M (SD), y	12.6 (3.5)
SBP, M (SD), mm Hg	135.4 (18.0)
Body mass index, M (SD), kg/m^2	28.4 (6.0)
Smoking status, *n* (%)	
Current	797 (12.8)
Former	2,508 (40.4)
Never	2,902 (46.8)
Chronic medical conditions[a], M (SD)	1.1 (0.9)
Use of antihypertensives, *n* (%)	3,970 (64.0)
Psychosocial measures, M (SD)	
Depressive symptoms	1.5 (2.0)
Neuroticism	5.3 (2.3)
Social engagement	2.6 (1.7)
Social network size	1.7 (6.4)
Cognitively stimulating activities	3.2 (0.7)
Perceived Stress score[b], M (SD)	5.2 (3.3)
Global cognitive score, M (SD)	0.3 (0.7)

M = mean; SD = standard deviation; SBP = systolic blood pressure.
n = 6207 but ranged from 6101 to 6207 for any given characteristic because of missing values on some variables.
[a] Chronic medical conditions included self-reported history of six conditions: history of heart disease, stroke, diabetes, cancer, hypertension, and hip fracture.
[b] Higher scores indicate greater reported stress; range, 0 to 18.

but the association remained highly significant ($p < .001$; Model 4). In the fully adjusted model, all covariates except sex, SBP, former smoking status, depressive symptoms, and social network size were statistically significant (data not shown). As evidenced by the very small changes in the stress × time interaction across models depicted in Table 2, none of the covariates had much effect on the impact of stress on rate of cognitive decline.

Mixed-effects regression models with the individual cognitive tests as the outcomes showed that the magnitude of the effect of stress on each test was nearly identical to the main effect of stress seen with the global cognition measure. In unadjusted models, each 1-point higher perceived stress score was related to an approximately 0.03-unit lower score on each individual cognitive test (range, −0.026 to −0.049; all $p < .001$). In a model that included demographic variables ("Model 2" covariates as described in the "Data Analysis" section), these associations remained significant (East Boston Story immediate recall: $B = -0.020$, SE = 0.003, $p < .001$; East Boston Story delayed recall: $B = -0.019$, SE = 0.003, $p < .001$; MMSE: $B = -0.014$, SE = 0.002, $p < .001$; Digit Symbol Modalities test: $B = -0.023$, SE = 0.003, $p < .001$). In addition, significant stress × time interactions were observed for the East Boston Story, both immediate ($B = -0.0013$, SE = 0.0005, $p = .014$) and delayed recall ($B = -0.0013$, SE = 0.0005, $p = .013$), and the MMSE ($B = -0.0027$, SE = 0.0005, $p < .001$) but not for the Symbol Digit Modalities test ($B = 0.0004$, SE = 0.0004, $p = .26$). This same pattern of findings was evident and changed a little, in risk factor–adjusted models (data not shown).

We also conducted sensitivity analyses excluding those with the poorest cognitive function at baseline to examine the possibility that feelings of stress that might arise from perceptions of poorer or declining cognitive skills with age could be influencing the findings. We found no evidence of such an effect; excluding 5%, 10%, or even 15% of respondents with the lowest global cognitive function score at baseline produced results identical to what we observed in the full sample (data not shown).

DISCUSSION

In this population-based cohort study of more than 6200 elderly blacks and whites, we found that higher levels of perceived stress were related to lower cognitive function as well as accelerated cognitive decline over nearly 7 years of follow-up. The observed associations remained after controlling for sociodemographic variables, vascular risk factors and chronic medical conditions, and psychosocial factors. Patterns of association were similar for the measure of global cognition and the four individual cognitive tests. These results suggest that increased levels of perceived stress may contribute to poorer global cognitive function in a diverse sample of adults 65 years and above.

We are not aware of previous studies in the population that have examined the association of self-reported perceived stress with level or rate of change in cognitive function. In one population study of persons aged 55 to 85 years, a differential effect of types of negative life events on cognition was reported, with the death of a child or grandchild being associated with cognitive decline, whereas chronic events, such as illnesses or conflicts were associated with better cognitive function (37). In a

TABLE 2. Effects of Time and Perceived Stress on Cognitive Function as Estimated From Mixed Models

	Model 1			Model 2			Model 3			Model 4		
	B	Standard Error	*p*	*B*	Standard Error	*p*	*B*	Standard Error	*p*	*B*	Standard Error	*p*
Time, y	−0.0402	0.0024	<.001	−0.0501	0.0024	<.001	−0.0504	0.0024	<.001	−0.0502	0.0024	<.001
Perceived stress	−0.0379	0.0025	<.001	−0.0206	0.0021	<.001	−0.0203	0.0021	<.001	−0.0068	0.0023	.004
Perceived stress × time	−0.0015	0.0004	<.001	−0.0014	0.0004	<.001	−0.0013	0.0004	<.001	−0.0013	0.0004	.001

previous report from the CHAP cohort, the presence of the stress-prone personality trait of neuroticism was associated with cognitive decline over a 5-year period (32). The present results build on these findings by showing that the effect of perceived stress on cognition was independent of personality or other indicators of psychosocial functioning and that the intensity or level of stress was associated with cognitive decline in the elderly.

It is possible that socioeconomic status (SES) influences both perceptions of stress and cognitive decline. As noted, we did see a small, inverse correlation between perceived stress and education in our cohort ($r = -0.17$). We further examined the association of stress with alternate SES indicators available in CHAP, including composite measures of adult SES (based on education, income, and primary occupation during adulthood) and lifetime SES (adult SES + parental education and family financial situation when participants were children; data not shown). These SES measures also were inversely related to perceived stress (both $r = -0.198$). Importantly, however, there was no indication of differential effects of stress on cognitive decline as a function of SES (i.e., no stress × education interaction). Thus, although it certainly is plausible that reported stress levels vary by SES, there is little evidence in our cohort for a meaningful impact of SES on stress-related cognitive decline over time.

We further considered whether our findings could be biased by mortality rates for this sample, given that all participants were at least 65 years old at the start of the study and more than 60% of our cohort was black. Life expectancy at age 65 years is known to be shorter in blacks than in whites (38). However, a previous report from CHAP (39) noted that the proportion of whites (31%) who passed away in the first 5 years of follow-up was slightly *higher* than the proportion of blacks (27%) who passed away. In addition, as noted, nearly two-thirds of our respondents completed at least three cycles of data collection, which occurred, on average, 3 years apart. Together, this information suggests a robust survival rate within our sample and little indication that the observed stress-related decline in cognitive function was unduly influenced by differential mortality rates.

There are several biologically plausible mechanisms that could link stress to aging and changes in cognition in old age (40). Repeated or chronic exposure to stress activates the hypothalamic-pituitary-adrenal axis and stimulates the release of glucocorticoids (41). Elevated glucocorticoid levels can contribute to long-lasting functional and structural changes in the brain, which may be pronounced or enduring during critical stages of the life course, for example, old age (41,42). Chronic stress also induces the release of inflammatory and hormonal indicators of accelerated aging (11,37,42,43) in addition to causing alteration in telomere length (44**)**. Telomeres are often considered an indicator of biological age, and stress has been shown to influence the rate of telomere shortening. Shortened telomere lengths have also been implicated in many aspects of cardiovascular disease (45–47) and also noted to predict early mortality in a community sample of adults 65 years and older (48). Unfortunately, we were unable to evaluate these mechanisms in the current study so we cannot determine their role in the relation between stress and cognitive decline. This remains a task for future studies.

Although the specific pathways underlying our observed findings remain to be determined, our data do provide important new evidence from a population-based study of the impact of stress exposure on brain functioning and cognition. These findings have potential clinical implications; especially because very high levels of stress appear to accelerate cognitive aging, evaluations of older adults presenting with complaints of changes in cognition should include careful assessments of stressful experiences. Future work also will need to examine whether stress reduction techniques, for example, yoga or mindfulness meditation, hold promise for ameliorating the effects of chronic stress on cognitive performance in adults as they age.

Our study does have limitations. We used a brief measure of perceived stress that was assessed only at one data cycle. The PSS asks respondents to consider experiences over the past month, but it does not ask respondents to report specific sources of stress or how long they have experienced a given stressor; thus, the scale does not allow us to distinguish between acute and chronic experiences of stress. Consequently, we were unable to determine if changes in perceived stress affected cognition or changes in cognition over time. Also, our population is from an urban setting in the Midwest, and the findings may not be generalizable to the aging populations in other types of settings in the United States. However, these limitations are offset by notable strengths of our study. First, these data come from a geographically defined sample of adults 65 years and older, with a wide range of SES backgrounds. Second, we use a composite measure of cognitive function that assessed a range of cognitive function administered at regular intervals with high follow-up participation. Third, we had up to five waves of data collection over an average of 6.8 years, allowing greater precision in measuring change over time. Finally, we considered other important factors in our analysis that might have influenced the association between stress and cognitive function by including depressive symptoms, psychosocial factors, and chronic health conditions

In sum, these data from a population-based sample of black and white adults 65 years and older offer important epidemiologic evidence of the relation between stress and decline in cognitive function. Understanding how the effects of stress affect cognition and whether preventing excessive stress could mitigate cognitive decline in old age could have substantial public health importance.

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