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## Inflammation and cognitive functioning in African Americans and Caucasians

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### Abstract

**Objective**—To examine associations between inflammation and cognitive performance in African Americans and Caucasians.

**Methods**—The sample included 59 African Americans and 219 Caucasians 50 years old who had a baseline visit at the Emory/Georgia Tech Center for Health Discovery and Well Being. Peripheral levels of inflammation (interleukin-6, interleukin-8, C-reactive protein, and tumor necrosis factor- $\alpha$ ) were examined in relation to performance on tests of visual processing (Identify the Odd Pattern), attention (Digit Span Forward), visuomotor set shifting (Digit Symbol Substitution), verbal set shifting (Digit Span Backwards), and memory (Recall a Pattern).

**Results**—Multiple regression models adjusting for potential demographic and vascular/metabolic confounders were conducted, with markers of inflammation included as either continuous or categorical (quartiles) variables. There were significant interactions between IL-8 and race for the Recall a Pattern ( $p = .006$ ) and the Digit Symbol Substitution ( $p = .014$ ) tests. Race-specific analyses (using a continuous variable for IL-8) demonstrated slower response times on the Recall a Pattern and Digit Symbol Substitution tests for African Americans but not for Caucasians. Categorical analyses among African Americans indicated that all of the top three quartiles of IL-8 were associated with slower reaction times on the Recall a Pattern test compared to the lowest quartile, while for Digit Symbol, the highest quartile of IL-8 was associated with the slowest cognitive performance.

**Conclusions**—These preliminary findings suggest a stronger association between IL-8 and cognitive performance in African Americans than Caucasians. This relationship should be further examined in larger samples that are followed over time.

### Keywords

inflammation; cytokines; African Americans; race; cognition

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Conflict of interest

None declared.

## Introduction

Inflammation is a risk factor for neurodegenerative disorders including Alzheimer's disease, as well as for the cognitive changes associated with normal aging. Both clinic and community based studies have demonstrated an inverse relationship between global cognitive status and specific domains such as memory, executive functioning, and processing speed and peripheral levels of inflammation including C-reactive protein (CRP) (Bettcher et al., 2012; Noble et al., 2010), interleukin-6 (IL-6) (Alley et al., 2008; Marsland et al., 2006; Mooijaart et al., 2013), interleukin-8 (IL-8) (Baune et al., 2008), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Holmes et al., 2009), although negative results have been obtained as well (see Gorelick, 2010 and Simen et al., 2011 for reviews). Several mechanisms have been hypothesized as driving the positive associations, including cytotoxicity from prolonged inflammation which, in turn, stimulates beta amyloid peptide production (Bermejo et al., 2008), and the influence of inflammation on structural brain changes (Jefferson et al., 2007; Satizabal et al., 2012). Jefferson et al. (2007) observed a significant association between higher levels of CRP and smaller total brain volumes as measured via magnetic resonance imaging in 1926 participants between 35 and 85 years old in the Framingham Heart Study. Similar associations were also found for TNF- $\alpha$  levels in a subset of participants ( $n = 1430$ ). These findings were recently replicated for baseline values of CRP in 1841 community residing adults 65 years and older participating in a three center study conducted in France (Satizabal et al., 2012). Satizabal and colleagues (2012) observed that higher CRP levels as well as higher IL-6 levels were associated with lower volumes of cerebral gray matter and higher volumes of total and periventricular white matter hyperintensities (WMHs). Additionally, higher IL-6 levels were linked with decreased hippocampal volume. Associations between these inflammatory measures with longitudinal changes in brain volume and WMHs, however, were not found at a 4-year follow-up.

Racial differences in levels of CRP, with higher values for African Americans, have been found in some studies (Albert et al., 2004; Khera et al., 2005; Paalani et al., 2011).<sup>18–20</sup> Paalani et al. (2011) published findings on levels of CRP, IL-6, and TNF- $\alpha$  and an anti-inflammatory cytokine (IL-10) in 191 African Americans and 314 Caucasians. These participants were Seventh Day Adventists and thus did not have risk factors such as tobacco and alcohol use that are themselves associated with inflammation. After controlling for possible confounders of the relationships between race and cytokine levels, the investigators found that race remained a significant predictor of IL-6 levels alone. IL6 has been found to be elevated in persons with vascular dementia (Zuliania et al., 2007). Since hypertension is more prevalent and under poorer control in African Americans than Caucasians (Egan et al., 2010), the finding of higher IL-6 levels in the former group is consistent with its association with vascular health. Jordanova et al. (2007) observed an association between IL-6 and cognitive performance in an African-Caribbean community residing sample of 290 persons aged 55–75 years old. Higher baseline values of serum IL-6, but not CRP, were associated with a decline in orientation and immediate word recall on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al., 1989) neuropsychological battery at an average follow-up at 34 months. A Caucasian comparison group was not included. In contrast, Yaffe et al. (2003) did evaluate possible differential influences of IL-6, CRP, and

TNF- $\alpha$  on cognitive performance as a function and race. There were no significant interactions between the markers and race on the Modified Mini-Mental State Examination (Teng and Chui, 1987) over a 2-year follow-up.

The purpose of the current study was to examine associations between inflammation and cognitive performance in African Americans and Caucasians. We took advantage of a database of individuals enrolled in the Emory/Georgia Tech Center for Health Discovery and Well Being (Brigham, 2010; Rask et al., 2011). The Center was established in 2008 to provide a model of preventive care for healthy participants and to develop a database and tissue sample repository. In our study, we sought to determine if levels of CRP, IL-6, IL-8, and TNF- $\alpha$  were correlated with measures of cognitive functioning in African Americans and Caucasians. Computer-administered tests allowed for an examination of reaction time indices which may be more sensitive to subtle processing differences as opposed to accuracy scores which are susceptible to ceiling effects in cognitively normal individuals. Given the previous finding of an association of IL-6 with cognitive processing in African Americans (Jordanova et al., 2007), it was hypothesized that this relationship would be replicated.

## Methods

### Subjects

Details concerning the Center are discussed elsewhere (Brigham, 2010; Rask et al., 2011). As part of the Center's recruitment methodology, a list of Emory University employees 18 years and older was generated after stratification to obtain a representative balance among faculty and staff. Every 10th employee was sent an e-mail invitation. Approximately 30% agreed to be contacted for screening, and 10% of these persons were subsequently enrolled. Exclusion criteria were a history in the past year of hospitalization except for accidents, severe Axis 1 psychosocial disorder, addition of new prescription medications to treat a chronic disease (except for changes in antihypertensive or antidiabetic agents), drug abuse or alcoholism, a current active malignant neoplasm, uncontrolled or poorly controlled autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, infectious, inflammatory, musculoskeletal, neurological, psychiatric, or respiratory disease, and any acute illness in the 2 weeks before baseline studies. The Emory University Institutional Review Board approved the protocols, and informed consent was obtained from all participants.

### Cognitive measures

Commonly employed versions of neuropsychological measures were administered via computer, using software developed by Aharonson and Korczyn (2004) and Aharonson et al. (2007) who found that performance assessed via reaction time data was sensitive to individuals with mild cognitive impairment and those who converted to dementia. These subtests included (1) Identify the Odd Pattern: Three patterns, each drawn within a square grid, were presented simultaneously, and the subject chose the pattern that did not match the other two by pressing one of three numbers on a keyboard; (2) Recall a Pattern: A pattern appeared in the center of the screen and then disappeared, followed by a 5-s delay after which three patterns were displayed. The subject chose the pattern just seen by pressing one

of three numbers on a keyboard; (3) Digit Symbol Substitution Task: A grid of nine boxes, consisting of unique symbols paired with the numbers 1–9, appeared on the top of the screen. A second grid was presented below, comprised of symbols but without their corresponding numbers. The subject was instructed to choose the numbers that were associated with each symbol, proceeding from left to right. Ninety seconds was allowed to complete the task; (4) Digit Span: The subject saw a string of numbers presented on the screen. After they disappeared, the subject attempted to replicate the string in either the same or the reverse order by pressing the corresponding numbers on the keyboard.

### Vascular/metabolic and inflammatory measurements

During a separate visit from the administration of the cognitive tests, subjects fasted 12 h and underwent venous blood collection. Serum measurements of levels of high-density lipoprotein cholesterol and glucose were obtained. Plasma was frozen at  $-70^{\circ}\text{C}$  for subsequent measurement of inflammatory markers (IL-6, IL-8, CRP, and TNF- $\alpha$ ) via Multiplex kit (R&D Systems, Minneapolis, MN). Subjects also underwent measurement of resting blood pressure and body mass (weight, height, and waist circumference).

### Analyses

We first assessed univariate correlations between markers and cognitive tests using Spearman correlation. Linear regression analyses using SAS PROC GLM were then conducted to test whether the association between inflammatory markers and cognitive functioning differed by race at time of baseline testing (longitudinal data on the cognitive tests were available only for a small percentage of subjects). Residuals were approximately normally distributed. Multiple regression models, controlling for potential confounders, were used to examine relationships between the inflammatory cytokines and cognitive functioning, with a main effects model and a second model with an interaction term included for race. The main effects models included markers as continuous terms as well as categorical terms (quartiles). Analyses using categorical data allowed us to visualize the shape of the exposure response (i.e. test performance) as monotonic or near monotonic, with continuous variables serving as a test of linear trends. For the interaction models, continuous markers were used; if the interaction was significant, we explored this further by using race-specific models with categorical and continuous markers. Twenty correlations evaluating relationships between the markers and tests were conducted separately for African Americans and Caucasians. In addition, 20 regression analyses were performed to examine relationships of race and their interaction with inflammatory markers on test performance. The threshold P-value for declaring significance using a false discovery rate approximation was adjusted such that the threshold P-value for determining statistical significance was  $a(m + 1)/2m$ , where  $a$  is the original conventional threshold of 0.05, and  $m$  is the number of tests (Benjamini and Hochberg, 1995). Thus, a threshold P-value of  $.05[(20 + 1)/(2 \times 20)]$ , or .026 was used.

Errors were infrequent (<1%) on the cognitive measures, similar to findings by Aharonson and Korszyn (2004) and Aharonson et al. (2007), and therefore the analyses used mean reaction times (in milliseconds) for each subtest as the dependent variable.

## Results

Data were available for 278 participants 50 years old who had blood drawn and cognitive tests administered an average of 28.4 (SD = 0.13) days of each other. Of these participants, 219 (78.6%) were Caucasians. We compared baseline demographic characteristics, cardiovascular risk factors and inflammatory biomarkers between African Americans and Caucasians (Table 1). African Americans were significantly younger and had lower educational attainment and lower representation of males. There were no significant differences in the percentage of African American vs. Caucasians with clinically elevated cutoffs for blood pressure, glucose, cholesterol, or body mass indices (Chobanian et al., 2003; NCEP, 2002; WHO, 2000, 2003). However, analyses of actual values revealed that Caucasians had higher fasting glucose levels ( $p < .001$ ).

### Correlations between inflammatory biomarkers and cognitive functioning

Table 2 shows the univariate Spearman product moment correlation coefficients between inflammatory markers and performance on the cognitive measures as a function of race. For Caucasians, there was a significant association between higher levels of IL-6 and slower reaction time on the Identify the Odd Pattern test ( $p = .01$ ) and a trend in a similar direction of the Digit Symbol Substitution test ( $p = .03$ ). For African Americans, correlations were nonsignificant.

### Regression analyses

Age, education, and gender were significant ( $p < .026$ ) predictors of many of the cognitive outcomes, and were themselves significantly different between African Americans and Caucasians. Other covariates suspected potentially of being confounders (hypertension, hypercholesterolemia, diabetes, and BMI) were initially included, but none turned out to be associated with any outcome at the  $p < 0.10$  level. Hence, they were not incorporated in the final models. Models using untransformed and transformed values of the inflammatory markers yielded similar results, and therefore untransformed values are reported.

Table 3 shows the results of multiple regression analyses examining relationships between inflammatory markers and race on processing speed. Examining the inflammatory markers as continuous variables, none were significantly associated with the cognitive measures. Model fit (R-squares) for main effects models was strongest for Identify the Odd Pattern (0.20), Recall a Pattern (0.16), and Digit Symbol Substitution (0.20), and weakest for Digit Span Forward (0.06) and Backward (0.08). Results examining the inflammatory markers as quartiles demonstrated significant monotonic findings for Digit Symbol and Digits Backwards for IL-8, Digit Symbol and Digit Span Forward for IL-6, and Identify the Odd Pattern, Recall a Pattern, and Digit Span Forward for CRP, which all increased across increasing quartiles. African Americans had overall significantly slower (higher) ( $p < .001$ ) scores on the cognitive tests than Caucasians.

Table 3 also shows the findings for analyses of the interactions between inflammatory markers and race on processing speed for the various cognitive measures. There was a significant interaction between IL-8 and race for the Recall a Pattern measure ( $p = .006$ ) as

well as for the Digit Symbol Substitution ( $p = .014$ ) test. Logged models gave similar results except the interaction terms were somewhat weaker for IL-8/Recall a Pattern ( $p = 0.02$ ) and IL8/Digit Symbol Substitution ( $p = 0.10$ ). Racespecific analyses (Tables 4 and 5) (using a continuous variable for IL-8) demonstrated slower response times on the Recall a Pattern ( $p = 0.034$ ) and Digit Symbol Substitution ( $p = 0.018$ ) tests for African Americans but not Caucasians. Categorical analyses of these two outcomes among African Americans indicated that all of the top three quartiles of IL-8 had slower reaction times on the Recall a Pattern test compared to the lowest quartile, while for Digit Symbol, only the highest quartile of IL-8 was associated with the slowest cognitive performance.

## Discussion

Results of this preliminary study indicated a significant interaction of IL-8 and race on cognitive processing, such that as levels of IL-8 increased, African Americans demonstrated slower reaction times on delayed memory and visuomotor set shifting tasks, whereas this relationship was not significant for Caucasians. To our knowledge, race as a possible modifier of the relationship between inflammation and cognitive functioning has not been previously investigated, with the exception of a study by Yaffe et al. (2003). These researchers examined the association between performance on the Modified Mini-Mental State Examination (3MS) and baseline inflammatory markers in a sample of 3,031 Caucasians and African Americans ages 70–79 years old who were enrolled in the Health, Aging, and Body Composition Study. While both CRP and IL-6 were predictive of worsening scores over 2 years, the association was comparable for both races. Unlike the present study, the 3MS does not include timed measures which may be especially sensitive to subtle processing differences in individuals who are otherwise cognitively intact. In addition, the 3MS provides a composite score versus a more fine grained assessment of individual cognitive domains.

The finding of a selective influence of IL-8 on cognitive processing is consistent with the results of a cross sectional study by Baune and colleagues (2008). These investigators examined the association between cytokines and cognitive performance in a sample of 369 community residing, elderly individuals enrolled in the Memory and Morbidity in Augsburg Elderly (MEMO) Study. Three of the serum cytokines were the same as in the current investigation, including IL-8, IL-6, and TNF- $\alpha$ . In addition, the study measured similar cognitive domains including memory and visuomotor set shifting speed. Only IL-8 was associated with cognitive performance, such that higher levels predicted poorer memory and slower processing speed. Baune et al. suggested that IL-8 is a marker of chronic inflammation, in contrast to other cytokines which may reflect transient changes and are themselves cleared within a few hours. As applied to our study, if IL-8 does measure more long-term inflammatory processes, then it would make sense to see a relationship with cognitive performance assessed at a different time point.

Inflammatory levels were not significantly different between African Americans and Caucasians, in contrast to other studies finding higher levels of CRP and IL-6 in the former group (Albert et al., 2004; Khera et al., 2005; Paalani et al., 2011), as well the association between IL-6 and vascular health (Zuliania et al., 2007). In addition, cardiovascular risk

factors such as hypertension were comparable, in contrast to epidemiological findings of a higher burden in African Americans (Egan et al., 2010). Our sample was limited to relatively healthy individuals who were screened for participation in the Emory-Georgia Tech Center for Health Discovery and Well Being based on the absence of uncontrolled or poorly controlled cardiovascular illness in the preceding year. Moreover, participants were excluded if they had a recent acute illness in the past two weeks or hospitalization in the last year. This may have attenuated any potential disparities in levels of inflammation and other risk factors. As such, the generalizability of the findings is limited and requires replication in a more heterogeneous sample. Other limitations of this study include the small sample size of African Americans compared to Caucasians, thereby restricting firm conclusions regarding racial differences. The cross-sectional design also prevents an evaluation of cause–effect relationships. Nevertheless, these preliminary findings do raise the possibility of differences in responses to inflammatory biomarkers between African Americans and Caucasians that should be addressed in future studies. Given the findings of a higher prevalence (Alzheimer’s Association, 2010) and incidence (Evans et al., 2003; Katz et al., 2012; Tang et al., 2001) of Alzheimer’s disease in African Americans, it is important to determine whether the influence of inflammatory biomarkers on cognitive functioning varies as a function of race since this could provide insight into different etiological mechanisms and treatment targets.

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### Key points

- Inflammation is a risk factor for neurodegenerative disorders including Alzheimer's disease, as well as for the cognitive changes associated with normal aging.
- The current study examined whether the influence of inflammatory biomarkers on cognitive functioning varies as a function of race.
- Our cross-sectional study found a significant interaction between interleukin-8 (IL-8) and race on cognitive processing in non-demented community residing older adults, such that as levels of IL-8 increased, African Americans demonstrated slower reaction times on delayed memory and visuomotor set shifting tasks, whereas this relationship was not significant for Caucasians.
- These preliminary findings suggest that race is a modifier of the relationship between inflammation and cognitive functioning.

**Table 1**Baseline characteristics<sup>a</sup>

|   | Entire sample (n = 278) | African Americans (n = 59) | Caucasians (n = 219) | p value |
|---|-------------------------|----------------------------|----------------------|---------|
| Age, years                                | 57.4 ± 5.4              | 55.1 ± 3.9                 | 58.0 ± 5.6           | <.001   |
| Male gender, n (%)                        | 101 (36.3)              | 11 (18.6)                  | 90 (41.1)            | <.01    |
| Education years                           | 17.6 ± 2.4              | 16.4 ± 2.5                 | 17.9 ± 2.3           | <.001   |
| BMI, kg/m <sup>2</sup>                    | 28.0 ± 6.3              | 28.1 ± 6.4                 | 28.0 ± 6.2           | 0.88    |
| Obese, <sup>34</sup> n (%)                | 79 (28.4)               | 17 (28.8)                  | 62 (28.3)            | 0.59    |
| Systolic BP, mm Hg                        | 124.8 ± 15.9            | 127.0 ± 16.9               | 124.2 ± 15.7         | 0.23    |
| Diastolic BP, mm Hg                       | 77.8 ± 10.5             | 79.1 ± 10.8                | 77.4 ± 10.5          | 0.28    |
| Elevated BP, <sup>31</sup> n (%)          | 57 (20.5)               | 15 (25.4)                  | 42 (19.2)            | 0.55    |
| Total cholesterol, mg/dL                  | 200.3 ± 39.3            | 196.5 ± 39.6               | 201.3 ± 39.2         | 0.41    |
| Elevated cholesterol, <sup>33</sup> n (%) | 36 (12.9)               | 7 (11.9)                   | 29 (13.2)            | 0.40    |
| Glucose, mg/dL                            | 92.1 ± 16.7             | 87.4 ± 9.6                 | 93.4 ± 17.9          | <.001   |
| Elevated glucose, <sup>32</sup> n (%)     | 42 (15.1)               | 6 (10.2)                   | 36 (16.4)            | 0.23    |
| CRP, mg/l                                 | 0.3 ± 0.4               | 0.3 ± 0.3                  | 0.3 ± 0.5            | 0.40    |
| IL-6, pg/mL                               | 1.3 ± 2.0               | 1.8 ± 2.3                  | 1.2 ± 2.0            | 0.06    |
| IL-8, pg/mL                               | 10.6 ± 8.0              | 9.3 ± 4.7                  | 10.9 ± 8.6           | 0.07    |
| TNF-α, pg/mL                              | 4.3 ± 7.6               | 3.6 ± 2.1                  | 4.5 ± 8.4            | 0.13    |

<sup>a</sup>BMI = body mass index; BP = blood pressure; CRP = C-reactive protein; IL-6 = interleukin 6; IL-8 = interleukin 8; TNF = tumor necrosis factor

Spearman correlation coefficients between levels of inflammatory biomarkers and reaction times on cognitive measures<sup>a</sup>

**Table 2**

|                           | CRP  |      | IL6  |                  | IL8 |      | TNF- $\alpha$ |      |
|---------------------------|------|------|------|------------------|-----|------|---------------|------|
|                           | AA   | C    | AA   | C                | AA  | C    | AA            | C    |
| Identify Odd Pattern      | -.02 | .11  | -.19 | .17*             | .15 | .10  | -.04          | -.03 |
| Recall a Pattern          | .06  | .09  | -.11 | .11              | .24 | .01  | -.01          | -.11 |
| Digit Symbol Substitution | -.04 | -.01 | -.15 | .15 <sup>+</sup> | .22 | .07  | .11           | -.08 |
| Digit Span Forward        | .05  | -.04 | -.04 | .08              | .08 | -.06 | .13           | -.09 |
| Digit Span Backward       | <.01 | .03  | -.01 | .04              | .19 | .07  | .20           | -.05 |

<sup>a</sup> Positive coefficients indicate that higher levels of the inflammatory markers are associated with longer (slower) reaction times

\* p < .01

+ p < .05

Table 3

Regression coefficients from multiple regression models (n = 278) with main effects and tests for interaction by race<sup>a</sup>

| Marker/test                     | Inflammatory marker: test for trend <sup>b</sup> (p-value) | Caucasians vs. AAs <sup>c</sup> (referent) (p-value) | Marker quartile 2 vs 1 <sup>d</sup> | Marker quartile 3 vs 1 | Marker quartile 4 vs 1 | Interaction term for race <sup>e</sup> (p-value) |
|---------------------------------|--|--|-------------------------------------|------------------------|------------------------|--|
| IL8/Identify Odd Pattern        | 2.2 ± 3.5 (0.53)   | -453.5 ± 72.4 (<0.001)                               | -70.6 ± 78.0                        | 109.3 ± 79.8           | 60.2 ± 78.5            | (0.14)   |
| IL8/Recall a Pattern            | -0 ± 2.4 (1.00)  | -265.3 ± 49.4 (<0.001)                               | -68.9 ± 53.4                        | 34.2 ± 54.6            | 7.2 ± 53.7             | (.006)   |
| IL8/Digit Symbol Substitution   | 3.9 ± 2.6 (0.13)   | -187.6 ± 52.6 (<0.001)                               | -50.7 ± 57.0                        | 9.1 ± 58.3             | 75.9 ± 57.4            | (.014)   |
| IL8/Digit Span Forward          | -1.0 ± 1.2 (0.24)  | -63.8 ± 24.2 (<0.01)                                 | -13.6 ± 26.2                        | 14.2 ± 26.8            | -30.7 ± 26.4           | (0.16)   |
| IL8/Digit Span Backward         | 5.5 ± 3.7 (0.14)   | -306.0 ± 75.6 (<0.001)                               | 48.5 ± 82.3                         | 89.8 ± 84.2            | 93.0 ± 82.8            | (0.10)   |
| IL6/Identify Odd Pattern        | 4.3 ± 14.0 (0.76)  | -447.5 ± 72.3 (<0.001)                               | 12.2 ± 79.2                         | -9.8 ± 80.6            | 88.3 ± 80.6            | (0.43)   |
| IL6/Recall a Pattern            | -4.0 ± 9.4 (0.66)  | -267.0 ± 49.3 (<0.001)                               | -3.7 ± 54.1                         | 37.0 ± 55.1            | 35.3 ± 55.0            | (0.66)   |
| IL6/Digit Symbol Substitution   | 8.8 ± 10.0 (0.38)  | -176.3 ± 52.7 (<0.001)                               | -17.1 ± 57.6                        | -15.8 ± 58.6           | 85.1 ± 58.6            | (.51)  |
| IL6/Digit Span Forward          | 1.8 ± 4.6 (0.70)   | -65.7 ± 24.2 (<0.01)                                 | -5.6 ± 26.5                         | 4.6 ± 26.9             | 34.2 ± 26.9            | (0.97)   |
| IL6/Digit Span Backward         | 11.0 ± 14.0 (0.44)   | -290.9 ± 75.7 (<0.001)                               | -18.1 ± 81.5                        | -31.1 ± 84.0           | 133.7 ± 83.9           | (0.48)   |
| CRP/Identify Odd Pattern        | -1.0 ± 65.0 (0.99)   | -448.9 ± 72.4 (<0.001)                               | -202.6 ± 90.8                       | 4.8 ± 74.7             | 61.5 ± 73.5            | (0.76)   |
| CRP/Recall a Pattern            | 14.0 ± 44.0 (0.76)   | -263.8 ± 49.3 (<0.001)                               | -111.9 ± 62.0                       | -20.2 ± 51.0           | 49.0 ± 50.2            | (.70)  |
| CRP/Digit Symbol Substitution   | -43.0 ± 48.0 (0.37)  | -180.5 ± 52.7 (<0.001)                               | -58.1 ± 67.0                        | -19.6 ± 55.1           | -33.7 ± 54.2           | (.63)  |
| CRP/Digit Span Forward          | -22.0 ± 21.0 (0.30)  | -70.1 ± 23.4 (0.01)                                  | -54.3 ± 29.7                        | -12.8 ± 24.4           | -2.9 ± 24.0            | (0.91)   |
| CRP/Digit Span Backward         | 31.0 ± 68.0 (0.65)   | -295.3 ± 75.7 (<0.001)                               | -77.7 ± 96.0                        | 53.5 ± 79.0            | 47.8 ± 77.7            | (0.13)   |
| TNF-α/Identify Odd Pattern      | -3.0 ± 3.7 (0.37)  | -445.5 ± 72.1 (<0.001)                               | 36.4 ± 78.2                         | 79.5 ± 79.6            | -81.5 ± 78.7           | (0.75)   |
| TNF-α/Recall a Pattern          | -3.0 ± 2.5 (0.30)  | -262.3 ± 49.2 (<0.001)                               | -10.7 ± 53.5                        | -20.1 ± 51.0           | -85.1 ± 53.8           | (0.41)   |
| TNF-α/Digit Symbol Substitution | -2.0 ± 2.7 (0.36)  | -177.1 ± 52.6 (<0.001)                               | -5.4 ± 57.2                         | 48.5 ± 58.2            | -58.1 ± 57.6           | 0.43   |
| TNF-α/Digit Span Forward        | -2.0 ± 2.7 (0.36)  | -65.4 ± 24.1 (0.01)                                  | -3.9 ± 26.4                         | -19.0 ± 26.8           | -13.8 ± 26.5           | (0.90)   |
| TNF-α/Digit Span Backward       | -2.0 ± 3.9 (0.54)  | -292.7 ± 75.6 (p < 0.001)                            | -1.2 ± 82.6                         | 49.5 ± 84.0            | -7.5 ± 83.0            | (0.32)   |

<sup>a</sup> All models adjust for age, gender, and education. Columns 2–6 are results for models with main effects only (no interaction term in model)

<sup>b</sup> A negative coefficient indicates that higher levels of the marker are associated with shorter (faster) reaction times, measured in milliseconds. No categorical variables (columns 4–6) included in this model.

<sup>c</sup> A negative coefficient indicates that reaction times, measured in milliseconds, are faster for Caucasians than African Americans on the cognitive measures.

<sup>d</sup> Cutoffs for quartiles determined by dividing the population into four equal-sized groups. No continuous variable for inflammatory markers included in this model using categories.

<sup>e</sup> The interaction term tests whether Caucasians and African Americans differ in the relationship between marker and cognitive test. The interaction term was added to the main effects model.

**Table 4**Coefficients for multiple regression models among caucasians<sup>a</sup>

| Marker(predictor)/test (outcome) | Inflammatory marker: test for trend <sup>b</sup> (p-value) | Marker quartile 2 vs 1 <sup>c</sup> | Marker quartile 3 vs 1 | Marker quartile 4 vs 1 |
|----------------------------------|--|-------------------------------------|------------------------|------------------------|
| IL8/Recall a Pattern             | -1.7 ± 2.3 (0.45)  | -157.1 ± 55.5                       | -.3.0 ± 55.8           | -72.0 ± 55.6           |
| IL8/Digit Symbol Substitution    | 2.1 ± 2.5 (0.41)   | -54.9 ± 62.0                        | 8.5 ± 62.2             | 22.9 ± 62.1            |

<sup>a</sup> All models adjust for Age, Gender, and Education.

<sup>b</sup> A positive coefficient indicates that higher levels of the marker are associated with longer (slower) reaction times, measured in milliseconds. No categorical variables for markers in this model.

<sup>c</sup> Cutpoints for quartiles determined by dividing the population into four equal-sized groups. No continuous variable for marker in this model.

**Table 5**Coefficients for multiple regression models among African Americans<sup>a</sup>

| Marker/test                   | Log of marker (test for trend) <sup>b</sup> (p-value) | Marker quartile 2 vs 1 <sup>c</sup> | Marker quartile 3 vs 1 | Marker quartile 4 vs 1 |
|-------------------------------|---|-------------------------------------|------------------------|------------------------|
| IL8/Recall a Pattern          | 23.0 ± 11.0 (0.034)                                   | 227.6 ± 136.9                       | 182.6 ± 154.4          | 268.2 ± 139.6          |
| IL8/Digit Symbol Substitution | 26.0 ± 11.0 (0.018)                                   | -66.5 ± 137.4                       | 17.0 ± 154.9           | 235.4 ± 140.0          |

<sup>a</sup> All models adjust for Age, Gender, and Education.

<sup>b</sup> A positive coefficient indicates that higher levels of the marker are associated with longer (slower) reaction times, measured in milliseconds. No categorical variables for markers in this model.

<sup>c</sup> Cutpoints for quartiles determined by dividing the population into four equal-sized groups. No continuous variable for marker in this model.