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Ruhee Patel April 9, 2019

Association between Anti-Inflammatory Interleukin-10 and executive function in African American Women at risk for AD

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Abstract

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Significance: The prevalence of AD differs by race: African-Americans (AAs) are two to four times more likely to be diagnosed with AD than non-Hispanic whites. AAs with elevated biomarkers of Alzheimer's Disease (AD), i.e., amyloid beta (Aβ) deposition, exhibit greater neurodegeneration in AD signature regions compared to non-Hispanic whites with elevated Aβ deposition (McDonough, 2017).

Objective: This thesis aims to examine whether inflammatory levels of interleukin-10 are associated with performance on executive function in 31 African American women at risk for developing AD because of parental history factors.

Design: Observational study comparing groups with elevated and normal interleukin-10 levels.

Participants: Study included 31 African-American women (age = 58.9 ± 8 years) with parental history of AD.

Measures: Inflammatory serum biomarkers and cognitive tests including Montreal Cognitive Assessment, Tower of London Test, Trail-Making Test, Timed Up and Go Test, and Color-Word Interference Test.

Results: Performance on Trail-Making Test differed between the elevated interleukin-10 group and the normal interleukin-10 group, with the elevated interleukin-10 group showing worse performance. There were no significant differences between groups on Tower of London Test, Timed Up and Go Test, Montreal Cognitive Assessment, and Color-Word Interference Test. There were significant differences between groups in levels of other inflammatory markers, including Interleukin-7 and interleukin-9 and interferon γ.

Conclusions: Although the exact relationship between AD and inflammation is not well defined, certain interleukins and cytokines, which also have genetic components, may incite inflammation and neuronal degradation (Weisman et al., 2006), leading to impaired aspects of executive function, e.g, set switching and inhibition. Further research should be conducted to continue investigating the relationship between inflammation, AD, and cognitive function.

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Introduction

As the average life expectancy of the United States population increases, prevalence of neurodegenerative diseases, such as Alzheimer's Disease (AD), also increase (McDonough, 2017). In 2010, 4.7 million Americans were reported to have AD, which is expected to increase to 13.8 million Americans by 2050 (Matthews et al., 2019). The prevalence of AD differs by race; African-Americans (AAs) are two to four times more likely to be diagnosed with AD than non-Hispanic whites. AAs with elevated biomarkers of AD, i.e., amyloid beta (Aβ) deposition, exhibit greater neurodegeneration in AD signature regions compared to non-Hispanic whites with elevated Aβ deposition (McDonough, 2017). In addition, environmental factors such as lower levels of physical activity and education have been found to increase risk of AD. These factors are more common in AAs and can influence cognitive decline (Sinha et al., 2018).

A genetic component to AD exists. Family history of AD, especially maternal history, is associated with increased levels of C-Pittsburgh Compound B standardized uptake value ratio (C-PIB SUVR). C-PIB SUVR measures the presence of Aβ deposition in the brain. Additionally, researchers conducted a study with neurotypical monozygotic and dizygotic twins of individuals with AD. Neurotypical dizygotic co-twins had normal low C-PIB SUVR, while the monozygotic neurotypical co-twins had levels of SUVR that were elevated to almost the same levels as those of the AD co-twins. These findings suggest genetic factors are involved in the development of Aβ (Chetelat et al., 2013).

Sex differences in cognitive decline

In addition to race and family history increasing the likelihood of developing AD, sex also impacts AD onset and age-related cognitive decline. Women have significantly faster age-related cognitive decline and greater levels of cognitive deterioration than men (Laws, Irvine, &

Gale, 2018). Gale et al (2016) assessed memory performance in healthy older adults, patients with mild cognitive impairment (MCI), and patients with AD. Results showed that among healthy controls, women out-performed men on an auditory verbal learning test and a visuospatial memory test in the intermediate and delayed versions. However, this advantage was not observed in MCI or AD patients. Women with AD performed worse than males with AD in all the tests (Gale, Baxter, & Thompson, 2016). Women are also at greater risk of developing AD. The apolipoprotein E4 allele, a genetic risk factor for developing AD, has been linked to increased risk of conversion from healthy aging to MCI, and MCI to AD in women (Laws, Irvine, & Gale, 2018).

Executive function

In older women, executive function may be predictive of future declines in memory and global cognition (Carlson, Xue, Zhou, & Fried, 2009). In a 9 year longitudinal study in older women, aged 74 years at baseline, 49% of the cohort developed cognitive impairment. Executive function impairment occurred three years before declines in memory. More clinical deficits in executive function developed than impairments in other domains of cognition. Memory declined at the same rate as executive function. Previous longitudinal research in older adults has shown that declined executive performance, related to inhibition and switching costs, was possibly caused by reduced connectivity between brain regions affected by the aging process (Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017). In addition to reduced connectivity, structural and functional neuroimaging studies in older adults have shown a preferential decline in the volume and function of prefrontal brain regions compared to other cortical areas. These changes are especially relevant to executive function, as the prefrontal cortex is involved in executive function (Glisky, 2007). Older adults without dementia often show declines in attention and

executive function. Although AD is characterized by difficulty in declarative memory, executive function has shown to be affected as well (Buckner, 2004). In a longitudinal study, executive function was shown to decline more rapidly in individuals who developed AD after 1.5 years compared to those who did not (Chen et al., 2001). Older adults (age 65+ years) studied over a four year period also exhibited differential changes in executive function over time. Participants who were later diagnosed with AD were significantly impaired in executive function compared to control individuals with normal cognition at baseline and follow-up as well as participants that had declines in executive function over time but did not meet the criteria for dementia at follow-up. The largest differences in executive function were seen between control individuals and participants who developed significant impairment during the study period and met the criteria for AD at follow-up (Albert, Blacker, Moss, Tanzi, & McArdle, 2007).

Inflammation and cognitive function

Chronic systemic inflammation puts individuals at risk for neurodegeneration and age-related cognitive decline. Although AAs bear a disproportionate burden of dementia compared to Whites, there are relatively fewer studies of inflammation and cognition that include AA participants (Windham et al., 2014). A clear link has been established between inflammation and cognitive function through research with several inflammatory markers. For example, elevated plasma interleukin-6 levels, which acts as both a pro-inflammatory cytokine and an anti-inflammatory cytokine, have been linked to an increased risk for later decline in cognition (Weaver et al., 2002). Further, different inflammatory markers have been linked to poorer cognitive function in specific groups. For example, the Healthy Aging Neighborhoods of Diversity across the Life Span study looked at inflammation and cognitive function in AA and white urban adults. Results showed that higher C-reactive protein (CRP) levels were linked to

worse baseline mental status in women younger than 50 years, and worse attention in older women and AAs (Beydoun et al., 2018).

Although the exact relationship between AD and inflammation is not well defined, certain interleukins (ILs) and cytokines, which also have genetic components, may incite inflammation and neuronal degradation. The current hypothesis is that Aβ stimulates the glial and microglial production of interleukins and other cytokines, leading to an ongoing inflammatory response resulting in synaptic dysfunction and neuronal death (Weisman, Hakimian, & Ho, 2006). The connection between AD and interleukin-10, which normally inhibits development and progression of chronic neurodegenerative disease, reveals mixed findings with some studies demonstrating better cognitive outcomes and diagnoses in association with higher interleukin-10 levels and some with lower interleukin-10 levels.

Inflammatory Biomarkers

Interleukins are secreted proteins that facilitate communication between leukocytes. Interleukins are grouped into families based on amino acid sequence homology, functional properties, or receptor chain similarities (Akdis et al., 2016).

Interleukin-10

Interleukin-10 is an anti-inflammatory cytokine produced by almost all innate and adaptive immune cells. Almost all leukocytes produce interleukin-10, including T and B cells, dendritic cells, mast cells, neutrophils, and more (Saxena et al., 2015). The strength of the interleukin-10 response reflects the strength of the preceding inflammatory biomarkers such as interleukin-6, interleukin-12, or interleukin-23 (Couper, Blount, & Riley, 2008). Its association with neurodegenerative disease is clear. Onset of inflammation in the brain and progression of prion disease was accelerated in mice that were interleukin-10 deficient when compared to

control mice (Richwine, Sparkman, Dilger, Buchanan, & Johnson, 2009). In addition, interleukin-10 is inversely associated with performance on tests of executive function and processing speed. Evidence suggests that the impact of inflammatory effects on executive function and episodic memory may be due to anatomical changes in the frontal and temporal lobes as well as the hippocampus. However, whether peripheral inflammation is a product of aging or a key force in progression of cognitive decline is unclear (Tegeler et al., 2016).

In an attempt to clarify the relationship between interleukin-10 and AD, investigators tested the association between cytokine expression in the brain and learning and memory deficits. Wild-type mice and interleukin-10 deficient mice were injected with lipopolysaccharide to induce an exaggerated inflammatory cytokine response in the brain. The mice deficient in interleukin-10 needed to swim further to locate a platform and were less efficient than the wild-type group at integrating new locations with previously learned information (Richwine et al., 2009). In relapse-remitting multiple sclerosis, proinflammatory cytokines such as interleukin-17A and TNF-α, along with decreased levels of interleukin-10 were associated with cognitive decline (Trenova et al., 2018). In a 2016 study, investigators measured cognitive function using a Stroop test battery and collected biomarker data in 96 older adults. Interleukin-10 was significantly lower in individuals with slower reaction times compared to individuals with faster reaction times in reading and naming interference tests (Fabregue & Butkowski, 2016). Additionally, in a study including healthy controls and AD patients in Northern Italy, the frequency of a specific nucleotide polymorphism of interleukin-10 (-1082A), which is associated with low production of interleukin-10, was significantly increased in AD patients.

On the other hand, high interleukin-10 levels have been associated with increased disease severity and worse survival rates in a variety of diseases, including lupus (Saxena et al., 2015)

and multiple myeloma (Wang et al., 2016). Excessive or mistimed interleukin-10 production can actually *inhibit* the proinflammatory response to the point where the trigger for inflammation is no longer controlled. If the sources and timing of interleukin-10 secretion do not align well with an infection, severe tissue damage may occur (Iyer & Cheng, 2012). Elevated levels of interleukin-10 was found to worsen amyloid plaque pathology and other AD relevant phenotypes in amyloid precursor protein transgenic mice models. Additionally, memory and learning worsened as interleukin-10 levels increased in mice models (Chakrabarty et al., 2015). In patients with early or late onset AD, there are significantly higher serum interleukin-10 levels (Fabregue & Butkowski, 2016). D'Anna et al. (2017) hypothesized that interleukin-10 may indicate a peripheral expression of Aβ deposition in patients with AD, as there was a significant negative correlation between interleukin-10 and an isoform of Aβ, Aβ42 (D'Anna et al., 2017).

As such, whether interleukin-10 levels are beneficial at elevated levels remains equivocal.

Other interleukins have a relationship with interleukin-10. Interleukins 7 and 9 are part of the common γ-chain family, which act as growth and proliferation factors and are involved in cell differentiation. Interleukin-7 is homeostatic cytokine that contributes to development of B and T cells and natural killer cells. Interleukin-9 is a growth factor for T cells and mast cells. Interleukin-8 is part of the α-chemokine family and is produced by cells after stimulation with other interleukins or tumor necrosis factor α (TNF α) (Akdis et al., 2016).

Monocyte chemoattractant protein-1 is a chemokine that is involved in regulating the migration and infiltration of monocytes and macrophages. It is produced constitutively or due to presence of cytokines or growth factors (Deshmane, Kremlev, Amini, & Sawaya, 2009), and its production is stimulated by interleukin-10 (Ikeda et al., 2002). Macrophage-derived chemokine

is a chemoattractant for lymphocytes, natural killer cells, dendritic cells, and monocytes, and may be involved in proinflammatory responses (Richter et al., 2014). C-reactive protein is part of the acute phase response to inflammation and tissue damage (Pepys & Hirschfield, 2003). C-reactive protein is produced in the liver in response to inflammatory cytokines such as tumor necrosis factor. Its concentration is proportional to the intensity of the preceding inflammation (Bray et al., 2016). Serum amyloid protein is the only molecule that is similar to C-reactive protein in terms of response speed and sensitivity (Pepys & Hirschfield, 2003). Serum amyloid protein is an acute-phase protein synthesized by the liver; it plays a unique role in immune activation and inflammatory cascades (Eklund, Niemi, & Kovanen, 2012).

Genetic Risk Factor: Apolipoprotein

Between 40% to 80% of AD patients have at least one Apolipoprotein E (ApoE) e4 allele. ApoE is produced by astrocytes in the brain and has three isoforms: ApoE e2, ApoE e3, and ApoE e4. ApoE is involved in lipid transport between astrocytes and neurons, Aβ clearance, blood-brain barrier support, and synaptogenesis (Tensaouti, Stephanz, Yu, & Kernie, 2018). The ApoE e4 allele is the strongest risk factor for developing AD. One e4 allele increases the risk of developing AD by 2 to 3 times while two e4 alleles increases risk by 12 times (Sinha et al., 2018). ApoE e4 carriers are 2.2 to 6.3 times more likely to develop MCI compared to non-carriers. In addition, ApoE e4 allele presence is associated with higher levels of AD-consistent pathology in individuals with subjective cognitive decline, including increased amyloid deposition, greater cortical atrophy, and possible white matter disruption (Ali, Smart, & Gawryluk, 2018). In mice models, ApoE deficiency and presence of ApoE4 lead to reduced dendritic spine density and less complex mature granule cells in the dentate gyrus (Tensaouti et

al., 2018). Pathological and neuroimaging studies have shown that lesions of AD may appear several decades before onset of AD in ApoE e4 carriers. Postmortem brains of 431 autopsies of subjects between 30 and 65 years of age showed that Aβ plaques started to appear in the fifth decade in patients who were ApoE e4 allele carriers. Carriers were also associated with increased levels of insoluble Aβ42 in tissues. In the sixth decade, Aβ plaques started to appear in individuals who were not ApoE e4 carriers. In addition, 80% of ApoE e4/4 carriers and 42% of ApoE e3/4 carriers had Aβ deposits between the ages of 40 and 49 (Pletnikova et al., 2018).

The hereditary component of AD differs by race. For example, by age 85, relatives of AAs with AD are 1.6 times more likely to develop dementia than relatives of Whites. In addition, the presence of two ApoE e4 alleles increases the risk of dementia in AA relatives by 1.8 times while that of whites increases by 1.5 (Green et al., 2002). The presence of one ApoE e4 allele increases risk of developing AD by 7 times compared with two ApoE e3 alleles in AAs (Graff-Radford et al., 2002). Overall, the prevalence of the ApoE e4 allele is higher in AAs than whites (Barnes & Bennett, 2014), as African Americans are 1.4 times more likely to carry the ApoE e4 gene variant compared to whites (Sinha et al., 2018). AAs usually present with an earlier age of onset, exhibit greater severity of symptoms, and are less likely than whites to receive treatments for AD (Barnes & Bennett, 2014).

There is a link between Interleukin-10 and AD with respect to Apolipoprotein E. The negative effects of interleukin-10 on Aβ proteostasis (maintaining the integrity of proteins), is connected to decreased Aβ phagocytosis by microglia, resulting in greater Apolipoprotein E expression and greater levels of its accumulation in insoluble amyloid plaques. The binding of Apolipoprotein E can decrease levels of Aβ aggregate clearance, which then promotes greater plaque deposition (Chakrabarty et al., 2015). Other studies have shown a significant elevated risk

of AD associated with an allele carrier associated with low interleukin-10 production in Europeans but not Asians, suggesting differences in risk factors among races (Magalhaes, Carvalho, Sousa, Caramelli, & Gomes, 2017).

This thesis aims to examine whether inflammatory levels of interleukin-10 are associated with performance on cognitive measures in 31 African American women at risk for developing AD because of parental history factors. We hypothesize that higher levels of interleukin-10 will be associated with decreased cognitive performance, specifically in several aspects of executive function. We are interested in executive function, e.g., planning/organization and switching/inhibition function because executive function is especially vulnerable in older populations and is highly important for the performance of activities of daily living. In addition, interleukin-10 levels have been inversely associated with composite scores of executive function and cognitive speed (Tegeler et al., 2016).

Methods

Thirty-one middle-aged African American women older than 40 were recruited from the Emory Alzheimer's Disease Research Center and from registries derived from previous studies of AD caregivers, given they are a population with a high likelihood of parental history of AD. The participants' parents had a diagnosis of probable AD as defined by National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria, which was verified using the validated Dementia Questionnaire and medical records when available (Hackney et al., 2019). Participant evaluations consisted of mobility and cognitive tests at Wesley Woods Health Center as well as blood draws at Emory Brain Health Center.

Participants underwent blood draws for inflammatory cytokines. Blood samples were collected after an 8-hour overnight fast by members of the research team. Measured biomarkers included those that have been linked to AD and family caregiver stress (Hackney et al., 2019), including interleukin 10. Four panels of biomarkers were measured in plasma using singleplex or multiplex assays in a Luminex 200 platform. Cognitive testing included evaluation of global and executive function, using the Montreal Cognitive Assessment (MoCA), the Trail-Making Test Parts A & B (Trails), the D-KEFS Color Word Interference Task (CWIT), and the D-KEFS Tower of London (TOL) task. Some scores are presented as raw scores and some scores have been converted into scaled values based on age group norms (Delis, 2001).

Cognitive Assessments

The Montreal Cognitive Assessment (MoCA) is a global cognitive screen for patients with mild cognitive impairment that measures visuospatial, executive function, language, attention, concentration and working memory. Visuospatial abilities are assessed through a task

where participants are required to draw a clock and a cube. Areas of executive functioning are assessed using the Trail making B task, a fluency task, and and a verbal abstraction task. Attention, concentration, and working memory are evaluated through a sustained attention task, serial subtraction task, and digit forwards and backwards task. Language is assessed through a naming task, fluency task, and complex sentences. Knowledge of place and orientation is also tested (Nasreddine et al., 2005). 30 is the highest possible score on the MoCA, although the definition of MoCA-indicated cognitive impairment has varied across studies. For example, some studies have defined cognitive impairment as a MoCA score of less than or equal to 22 and other studies have defined cognitive impairment as a MoCA score of less than or equal to 28 (Lim & Loo, 2018).

Conditions A and B of the Trail-Making Test, first introduced in 1938 by Partington, were administered to participants. Condition A requires participants to draw lines connecting numbers inside circles in numerical order. Condition B requires participants to draw lines connecting alternating numbers and letters in order. This test reflects several cognitive processes including attention, visual search and scanning, sequence and shifting, ability to execute and modify a plan of action, the ability to maintain different trains of thought at once, and fluid cognitive ability (Salthouse, 2011). The difference score between conditions A and B, which is B-A, was used as an outcome variable. Performance of Trail-Making Test Part B relative to performance on part A reflects the ability to switch between two tasks and efficiency in suppression of a task that was previously abandoned. The difference score between parts A and B provides information on task switching independently of motor speed and visual scanning speed (Arbuthnott & Frank, 2000).

The Color Word Interference Task contains color naming, color name reading, inhibition, and switching conditions. In the inhibition condition, participants are instructed to name the ink colors of the written words while ignoring the printed word. In the switching condition, participants switch between reading the ink colors and written words. Executive function components of inhibition and switching are able to be isolated because results control for color naming and reading, which are measured in participants in the first two conditions of the test (Fjell et al., 2017).

The Tower of London test is designed to measure frontal lobe function and executive function processes (Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012). Participants are instructed to build a tower from a starting position like the one shown to them in a picture. Only one piece can be moved at a time, and participants are not allowed to place a big piece over a smaller piece. Performance on the Tower of London requires coordination of distinct cognitive abilities that fall under executive function: planning an organized series of steps, goal-directed behavior, inhibition of inappropriate move selections and error monitoring. Working memory is also involved in this test (Rainville et al., 2012).

The Timed Up and Go test assesses both motor and cognitive function (Tomas-Carus et al., 2019). We used a cognitive measure from this test, Serial 3s Percent Correct, to assess working memory. Participants are given a number to start with and are given fifteen seconds to keep subtracting by three.

Statistical Analysis plan

Data from baseline observations from a cohort with parental history of AD assigned to participate in experimental and control arms of a longitudinal study were used to examine the

association between cognitive variables and interleukin-10 levels. Data were reviewed for normality and skew with the Shapiro-Wilk test.

The sample was categorized into elevated and normal interleukin-10 level groups through a literature-determined cutoff, which we explain here. A study assessing interleukin-10 levels in adults with Hodgkin's disease measured interleukin-10 levels in a group of 18 healthy control individuals for comparison. The mean serum level was 7.1 pg/ml with a standard deviation of 1.4 pg/ml. Based on these values, the upper limit of the normal range of interleukin-10 was determined by addition of two standard deviations to the mean, which was *10.1 pg/ml*. Therefore, interleukin-10 levels under 10 pg/ml were considered normal while values equal to 10 pg/mL or higher were categorized as elevated (Sarris et al., 1999). Another study, using a cutoff level of 10 pg/ml to divide a group of melanoma patients into two groups revealed significant differences in survival between the two groups. Mean survival rates of patients with interleukin-10 levels below 10 pg/ml was significantly higher than patients with interleukin-10 levels of 10 pg/ml or higher (Nemunaitis, Fong, Shabe, Martineau, & Ando, 2001). Because of these reports, we used a cutoff of 10 pg/ml for interleukin-10 levels to categorize the sample into elevated and normal interleukin-10 groups.

Descriptive statistics were calculated and compared between groups using t-tests or Fisher's exact tests. Spearman or Pearsons correlations were used to determine association of interleukin-10 level with cognitive variables for the entire sample, for the elevated IL-10 group and the normal IL-10 group, depending on the normality of the data. For non-normally distributed data, Mann-Whitney U tests and t-tests in the case of normally distributed data, were performed to determine significant differences between groups (elevated interleukin-10 and normal interleukin-10) on cognitive variables. Variables that had fewer than or equal to six levels

of frequency were dichotomized into categories such as “perfect performance” vs “some errors” for error scores, “100% rank” vs “lower than 100% rank” for rank scores, and “higher than 10” vs “lower than 10” for the scaled scores. These dichotomized variables were compared with the Fisher’s exact test, or chi square tests. Mann-Whitney U tests and independent t-tests were also used to determine level differences in the other biomarkers (interleukin-7, interleukin-8, interleukin-9, interferon γ, transforming growth factor α, tumor necrosis factor α, macrophage-derived chemokine, monocyte chemoattractant protein-1, c-reactive protein, and serum amyloid protein) between elevated interleukin-10 and normal interleukin-10 groups.

Data were analyzed with R software and SPSS (version 22).

Results

31 individuals with parental history of AD (all female; age 58.9 ± 8 years) were included in the sample. 19 individuals were caregivers while 12 were not. In our sample, ApoE status information was available for two individuals. Out of the two, an ApoE e4 allele was present in one individual.

Participants in the normal interleukin-10 group and the elevated interleukin-10 group did not differ significantly in education level, number of medications, occupational status, caregiver status, income, hours of sleep, and sleep quality (Table 1). However, participants in the interleukin-10 group and the elevated interleukin-10 group did show significant differences in inflammatory profiles. Individuals in the elevated interleukin-10 group had significantly higher levels of interleukin-7 ($p<0.01$), interleukin-9 ($p=0.011$), interferon γ ($p=0.005$), interleukin-8 ($p=0.044$), and transforming growth factor-α ($p=0.03$) compared to individuals in the normal interleukin-10 group (Table 2).

Participants in the normal interleukin-10 group performed significantly better on the difference between Parts A and B in the Trail-Making Test ($p=0.044$) compared to participants in the elevated interleukin-10 group (Figure 1). There were no significant differences between groups in the Montreal Cognitive Assessment, Serial 3s test, Color Word Interference Test, and Tower of London test (Table 3).

Table 4 shows correlations between interleukin-10 levels and cognitive variables for the whole sample, the normal interleukin-10 group, and the elevated interleukin-10 group. Several correlations were representative of moderate to large effects as per Cohen's conventions; however, none of the correlations were significant. Correlations were in the moderate range for the normal interleukin-10 group in Trails, MoCA, several of the Color Word interference Task

variables, including those related to errors and performance in inhibition and switching. Notable large correlations (e.g., $\rho > .500$) were noted in MoCA, and the Tower of London rule violations variables in the Elevated interleukin-10 group.

Discussion

This study examined the association between inflammatory levels and performance on measures of executive function in African-American women at higher risk of developing AD due to parental history of AD. Differences were found between groups with elevated versus normal levels of interleukin-10 in a very common test of inhibition/switching, the Trails B test. Inhibition and switching are one aspect of executive function. There were also differences between groups in levels of other inflammatory markers that are related to the function of interleukin-10. Further, correlations of moderate and large effect sizes were noted in various aspects of executive function, with inhibition and switching variables having moderate associations with normal interleukin-10 levels and planning/organization and global cognition having large effect on associations with elevated interleukin-10 levels.

Participants with elevated interleukin-10 levels showed significantly poorer performance on the Trail-Making Test compared to participants with normal interleukin-10 levels. Normative scores for the Trail-Making Test have been stratified by age and education level by Tombaugh et al. The normative Trails difference score for individuals in our sample is 37.02 seconds (Tombaugh, 2004). Individuals in the normal interleukin-10 group performed at about the normative level, at 37.3 seconds. Individuals in the elevated interleukin-10 group, however, performed significantly worse than the normal interleukin-10 group, at 51.3 seconds ($p=0.044$) (Table 3). Although this finding is not supported by similar effects on other tests of executive function in this sample, reduced performance on the Trails difference score suggests support for the hypothesis that increased interleukin-10 levels result in decreased cognitive performance. The nature of the cognitive variables may explain the difference in results between Trails difference and other measures of executive function. The trails difference is reported to the 0.01

second, while scaled scores and percentile ranks reported for the other cognitive variables are only reported as whole numbers.

Evidence suggests that Trail Making Test performance may be useful in detecting early dementia. Rasmusson, Zonderman, Kawas, & Resnick (1998) used previously reported dementia cutoff scores on Trail Making Test Part B, which resulted in correct classification of 89.4% of nondemented participants, 63% of participants with any cognitive dysfunction, and 72% of participants with dementia (Rasmusson, Zonderman, Kawas, & Resnick, 1998).

In order to investigate the relationship between cognition and functioning in daily life, researchers have examined how well executive functioning can be predictive of daily functioning. One hypothesis is that executive functioning may have the largest influence on daily functioning because it controls other aspects of cognition (Mitchell & Miller, 2008). Significant correlations have been measured between executive function and instrumental activities of daily living as well as advanced activities, including leisure and self-development activities (Cornelis, Gorus, Van Schelvergem, & De Vriendt, 2019). Previous research has shown a relationship between performance on the Trail Making Test and functional ability. In a study including 50 older adults, investigators measured executive function through several measures: the Controlled Oral Word Association test, the Wisconsin Card Sorting Test, and Trail Making Test Part B. Functional ability was measured with the Independent Living Scales, which allowed for objective assessment as opposed to questionnaires that may involve bias. The Independent Living Scales involve assessments of memory and orientation, managing money, managing home and transportation, health and safety, and social adjustment. Trail Making Test Part B and education were the only significant predictors of functional ability, while Trail Making Test Part B accounted for the most variance. Results showed that Trail Making Test Part B is particularly

sensitive to functional status, and this relationship suggests that complex daily activities, such as balancing a checkbook or cleaning a house, involve mental flexibility and psychomotor speed (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002). Trail Making Test Part B was also the best predictor of daily functioning when compared to the Tower of London test and measures of fluency. In this case, daily functioning was measured based on tasks of time orientation, communication, financial skills, grocery shopping, meal preparation, and more. Therefore, the Trail Making Test Part B shows promise as an initial screening for executive dysfunction (Mitchell & Miller, 2008).

In this study, set-shifting was isolated by subtracting Trail Making Test Part A from Part B. Previous studies that also isolated set-shifting have suggested a relationship between set-shifting and functional status. Nguyen, Copeland, Lowe, Heyanka, & Linck (2019) measured components of executive function including visuomotor set shifting using Trail Making Part B, verbal abstraction, nonverbal abstraction, and verbal fluency. Trail Making Test results were controlled for processing speed and visuomotor scanning, as Trail Making Test Part A score was included in the regression model. The Texas Functional Living Scale was used to measure instrumental activities of daily living and includes four subscales: time, money and calculation, communication, and memory. Only visuomotor set shifting and verbal abstraction significantly contributed to the Texas Functional Living Scale total score (Nguyen, Copeland, Lowe, Heyanka, & Linck, 2019). A difference score between Trail Making Test Part A and Part B was used to measure executive function in a sample consisting of normal controls, individuals with mild cognitive impairment, and mild AD patients. When assessing the entire sample, the Trails difference score was significantly associated with instrumental activities of daily living (Marshall et al., 2011). Processing speed may play an explanatory role in the connection between

the Trail Making Test and activities of daily living. Trail Making Test Part B is highly associated with measures of processing speed. In addition, processing speed and executive function have been considered a joint function. Processing speed has a limiting effect on cognition and independent activities of daily living (Karzmark & Deutsch, 2018).

The Trail Making Test has also been used as a screening measure for driving impairment in older drivers, both with and without cognitive impairment. Road testing consisted of specialists who rated participants' driving performance as safe, marginal, or unsafe. Performance on the Trail Making test was significantly correlated with impaired driving on road tests (Papandonatos, Ott, Davis, Barco, & Carr, 2015).

Changes in interleukin-10 levels have previously been documented in the prefrontal cortex with behavioral differences. For example, differences in interleukin-10 expression in the prefrontal cortex were found in a study examining the effects of ketamine on depressive-like behavior in rat models. Increased interleukin-10 levels in the prefrontal cortex were seen in rats that had induced depressive-like behavior through lipopolysaccharide. In contrast, rats that were treated with ketamine to reduce depressive-like behavior showed a significant increase in prefrontal cortex interleukin-10 levels (Yang et al., 2013). In addition, upregulation of interleukin-10 has been shown to be involved in inhibiting neuropathic pain in the ventrolateral orbital cortex in a dose-dependent manner (Shao et al., 2015).

Several inflammatory factors were significantly different in levels between groups. One of them, interferon γ is a cytokine that is secreted by activated T cells and natural killer cells. It promotes macrophage activation, coordinates innate immune system activation, and controls cellular apoptosis (Tau & Rothman, 1999). Transforming growth factor α binds to epidermal growth factor receptors, induces cell proliferation events such as wound healing and

embryogenesis (McInnes et al., 1998), and indirectly stimulates luteinizing hormone-releasing hormone (Ojeda, Ma, & Rage, 1997). Tumor necrosis factor α is produced by macrophages and regulates cell proliferation, survival, differentiation, and apoptosis. It is known as the "master-regulator" of inflammatory cytokine production, as it plays a key role in the cytokine cascade that is involved in inflammatory diseases (Parameswaran & Patial, 2010). The relationship between groups and levels of biomarkers may be explained by the following. Interleukin-10 inhibits production of both interferon γ and tumor necrosis factor α (Oral et al., 2006).

Other biomarkers, including monocyte chemoattractant protein-1, which production is stimulated by interleukin-10, Macrophage derived chemokine, CRP and SAP were not found to be significantly different between groups, which may be explained by their involvement in acute phase inflammation (Pepys & Hirschfield, 2003), as opposed to interleukins which are involved in leukocyte communication (Akdis et al., 2016).

None of the correlations of this study were significant, which is a limitation of a small sample size. In spite of the sample size limitations, several moderate to large correlations were noted in both groups in different aspects of cognitive function, i.e. inhibition/switching in the normal group and planning/organization variables in the elevated group. It is important to note that some variables, such as the Montreal Cognitive Assessment Score (Figure 1), the Color Word Interference Test - Inhibition/Switching Scaled Score (Figure 2), and the Tower of London Total Rule Violations Cumulative Percentile Rank (Figure 3) displayed conflicting correlation directions, meaning that while one would assume that normal interleukin-10 levels would lead to enhanced performance on cognitive variables, this was not always the case for these correlations. This result aligns with conflicting findings of previous studies on interleukin-10 levels and cognitive function, which largely present equivocal findings. However, conflicting findings were

not found in the elevated interleukin-10 group, with expected lesser cognitive performance related to higher interleukin-10 levels. Tegeler et al. (2016) previously reported significant inverse correlations between interleukin-10 levels and executive function. However, the average age of this sample was 68 ± 3.6 years, which is older than our sample (age 58.9 ± 8 years).

This study had several limitations. The study is likely underpowered to determine some effects due to the small sample size in both groups. In particular, our ability to detect significant correlations was limited in this study given the small sample. In addition, diabetes and hypertension both affect biomarker levels and may have impacted the results of this study in unknown ways. The effects of common medications such as statins also affects inflammatory levels which was not taken into account. The findings of this study emphasize the necessity for further studies on inflammation, executive function, and cognitive decline in African-American individuals.

Caregiver status was also not taken into account. Caregiver status may have an effect on inflammatory variables measured. Many studies have suggested a link between family caregiving and adverse mental and physical health consequences. However, family caregiving may also have positive effects on health and well-being. Several population-based studies have found longer lifespans for family caregivers compared to individuals who did not have family caregiver responsibilities (Roth et al., 2019). However, AD caregiving is associated with higher levels of subjective stress measures, as well as elevated levels of C-reactive protein and inflammatory cytokines (Aschbacher et al., 2007) (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012).

Another limitation is having examined only aspects of executive function in this cohort. Other tests of cognitive function measuring language, memory, attention, working memory and

visuospatial function should be included in future studies. Further, genetic data were available in a very small number of participants, allowing minimal conclusions to be made about the importance genetic components to developing AD and cognitive performance.

In conclusion, we present evidence that supports reduced cognitive performance in executive function in a cohort at risk for AD with elevated interleukin-10 levels. We also have noted evidence that continues to make conclusions equivocal regarding this matter. It is possible that some specific aspects of executive function are more affected than others. Future studies are needed to better clarify the relationship between inflammatory biomarker levels, AD, race, sex and cognitive performance.

Table 1. Characteristics of 31 African-American Women with Parental History of AD

Characteristics	Whole Sample (N=31) Mean (SD)/N (%)	Normal Interleukin-10 (N=17) Mean (SD)/N (%)	Elevated Interleukin-10 (N=14) Mean (SD)/N (%)	P-value
Age (years)	58.9 (7.97)	61.2 (8.88)	56.2 (5.9)	0.084
Highest Education Level				0.913
High school graduate/GED	1 (3.2)	0 (0)	1 (7.1)	
Vocational training	2 (6.5)	1 (5.9)	1 (7.1)	
Some college/Associates degree	5 (16.1)	3 (17.6)	2 14.3)	
Bachelor's degree				
Master's degree	14 (45.2)	8 (47.1)	6 (42.9)	
Doctoral degree	5 (16.1)	2 (11.8)	3 (21.4)	
	4 (12.9)	3(17.6)	1 (7.1)	
Number of Medications	5.1 (4.28)	4.2 (3.3)	6.1 (5.2)	0.246
Occupational Status				0.724
Work full-time	9 (29)	6 (35.3)	3 (21.4)	
Work part-time	4 (12.9)	2 (11.8)	2 (14.3)	
Retired	12 (38.7)	7 (41.2)	5 (35.7)	
Unemployed	2 (6.5)	1 (5.9)	1 (7.1)	
Disabled	4 (12.9)	1 (5.9)	3 (21.4)	
Caregiver*				1
Yes	19 (61.3)	10 (58.8)	9 (64.3)	
No	12 (38.7)	7 (41.2)	5 (35.7)	
Income				0.092
$19,000 or less	5 (16.1)	1 (5.9)	4 (28.6)	
$20,000-$39,000	6 (19.4)	4 (23.5)	2 (14.3)	
$40,000-$59,000	11 (35.5)	9 (52.9)	2 (14.3)	
$60,000-$79,000	2 (6.5)	1 (5.9)	1 (7.1)	
$80,000 or more	7 (22.6)	2 (11.8)	5 (35.7)	
Housing				1
House/Apt/Condo	29 (93.5)	16 (94.1)	13 (92.9)	
Relative's Home	2 (6.5)	1 (5.9)	1 (7.1)	
Use of Assistive Device for Walking				0.457
Some of the time	5 (16.1)	4 (23.5)	1 (7.1)	
Never	26 (83.9)	13 (76.5)	13 (92.9)	
Marital Status				0.867
Single	5 (16.1)	2 (11.8)	3 (21.4)	
Married/partnered	10 (32.3)	6 (35.3)	4 (28.6)	
Separated/divorced	13 (41.9)	7 (41.2)	6 (42.9)	

Widowed	3 (9.7)	2 (11.8)	1 (7.1)	

Menopause				0.699
Yes	20 (64.5)	12 (70.6)	8 (57.1)	
No	6 (19.4)	3 (17.6)	3 (21.4)	
Unsure	5 (16.1)	2 (11.8)	3 (21.4)	
Hormone Therapy				0.381
Yes	2 (6.5)	0 (0)	2 (14.3)	
No	29 (93.5)	17 (100)	12 (85.7)	
Exercise Frequency				0.358
Never	3 (9.7)	2 (11.8)	1 (7.1)	
Once a month	2 (6.5)	0 (0)	2 (14.3)	
1-4 times a month	7 (22.6)	5 (29.4)	2 (14.3)	
Greater than once a week	18 (58.1)	9 (52.9)	9 (64.3)	
Don’t know	1 (3.2)	1 (5.9)	0 (0)	
Angiotensin Converting Enzyme (ACE) Inhibitors				0.926
Yes	8 (25.8)	5 (29.4)	3 (21.4)	
No	23 (74.2)	12 (70.6)	11 (78.6)	
Beta Blockers				0.741
Yes	4 (12.9)	3 (17.6)	1 (7.1)	
No	27 (87.1)	14 (82.4)	13 (92.9)	
Aerobic Activity in the Past 4 Months				1
Yes	16 (51.6)	9 (52.9)	7 (50)	
No	15 (48.4)	8 (47.1)	7 (50)	
Past Smoking				0.724
Yes	11 (35.5)	7 (41.2)	4 (28.6)	
No	20 (64.5)	10 (58.8)	10 (71.4)	
Alcoholic Beverages in the Last Month				0.12
Yes	23 (74.2)	15 (88.2)	8 (57.1)	
No	8 (25.8)	2 (11.8)	6 (42.9)	
High Cholesterol				0.257
Yes	18 (58.1)	11 (64.7)	7 (50)	
No	11 (35.5)	6 (35.3)	5 (35.7)	
Unsure	2 (6.5)	0 (0)	2 (14.3)	
High Blood Pressure				1
Yes	20 (64.5)	11 (64.7)	9 (64.3)	
No	11 (35.5)	6 (35.3)	5 (35.7)	
Diabetes				0.272
Yes	5 (16.1)	3 (17.6)	2 (14.3)	
No	24 (77.4)	14 (82.4)	10 (71.4)	

Unsure	2 (6.5)	0 (0)	2 (14.3)	
History of Heart Attack				1
Yes	1 (3.2)	1 (5.9)	0 (0)	
No	30 (96.8)	16 (94.1)	14 (100)	
Weekend Hours of Sleep	6.3 (1.37)	6.4 (1.17)	6.2 (1.63)	0.740
Weekday Hours of Sleep	5.9 (1.47)	5.8 (1.36)	6.1 (1.64)	0.610
Sleep Quality in the Past Month				0.861
Excellent	2 (6.5)	1 (5.8)	1 (7.1)	
Very good	6 (19.4)	4 (23.5)	2 (14.3)	
Good	8 (25.8)	5 (29.4)	3 (21.4)	
Fair	9 (29.0)	5 (29.4)	4 (28.6)	
Poor	6 (19.4)	2 (11.8)	4 (28.6)	

Table 1. Characteristics of 31 African-American Women with Parental History of AD. Independent t tests were used to determine significant differences between groups on age, number of medications, weekend hours of sleep, and weekday hours of sleep. *Chi square test was used. Fisher's exact test was used for all other variables.

Table 2. Inflammatory Variables of 31 African-American Women with Parental History of AD

Variable		*M*	SD	*Mdn*	IQR	Q1	Q3	*p*
IL-10	Whole Sample	10.83	4.69	9.33	4.14	8.02	12.16	0.000
	Normal IL-10	7.73	1.38	8.09	2.01	6.75	8.76	
	Elevated IL-10	14.61	4.53	13.22	4.46	11.26	15.72	
IL-7*	Whole Sample	4.28	1.25	4.14	1.79	3.41	5.20	0.000
	Normal IL-10	3.58	0.8	3.55	1.07	3.08	4.15	
	Elevated IL-10	5.13	1.18	5.31	1.47	4.25	5.72	
IL-9	Whole Sample	0.56	1.01	0.08	0.44	0.08	0.52	0.011
	Normal IL-10	0.16	0.34	0.08	0.04	0.04	0.08	
	Elevated IL-10	1.06	1.31	0.46	1.6	0.08	1.68	
IFNγ	Whole Sample	11.72	6.97	9.84	6.77	7.35	14.12	0.005
	Normal IL-10	8.65	4.46	9	4.05	6.11	10.16	
	Elevated IL-10	15.45	7.77	13.15	9.54	10.04	19.57	
IL-8	Whole Sample	11.83	30.19	3.95	3.42	2.94	6.36	0.044
	Normal IL-10	3.86	1.56	3.42	2.13	2.87	5.00	
	Elevated IL-10	21.5	43.78	6.11	4.45	3.38	7.83	
TGFα	Whole Sample	1.22	1.46	0.61	1.48	0.21	1.69	0.030
	Normal IL-10	0.62	0.74	0.42	0.56	0.19	0.75	
	Elevated IL-10	1.95	1.78	1.48	2.75	0.58	3.33	
TNFα	Whole Sample	15.88	57.72	5.24	2.46	4.29	6.75	0.071
	Normal IL-10	23.8	78.09	4.83	1.45	4.04	5.49	
	Elevated IL-10	6.26	1.66	6.52	2.41	4.90	7.32	
MDC*	Whole Sample	932.34	344.26	940.89	343.65	727.61	1071.26	0.334
	Normal IL-10	877.69	359.04	880.89	329.27	720.88	1050.15	
	Elevated IL-10	998.7	325.87	962.03	326.02	812.05	1138.07	
MCP -1	Whole Sample	172	52.83	154.3	49.5	139.5	189.00	0.118
	Normal IL-10	164.38	53.2	144.13	23.01	136.05	159.06	
	Elevated IL-10	181.3	52.8	177	53.68	147.70	201.40	
CRP^	Whole Sample	0.37	0.46	0.2	0.32	0.10	0.41	0.302
	Normal IL-10	0.48	0.57	0.31	0.39	0.10	0.49	
	Elevated IL-10	0.24	0.24	0.18	0.18	0.08	0.26	
SAP*^	Whole Sample	0.27	0.09	0.26	0.13	0.20	0.33	0.516
	Normal IL-10	0.26	0.09	0.26	0.1	0.20	0.30	
	Elevated IL-10	0.29	0.11	0.26	0.16	0.21	0.38	

Table 2. Inflammatory Variables of 31 African-American Women with Parental History of AD Elevated = interleukin-10 ≥ 10 pg/ml; Normal = interleukin-10, 3-10 pg/ml; *Mdn* = median; *M* = mean; *SD* = standard deviation; IQR = interquartile range; Q1 = quartile 1; Q3 = quartile 3; IL=

interleukin; IFNγ = Interferon gamma; TGFα = Transforming growth factor alpha; TNFα = Tumor necrosis factor alpha; MDC = Macrophage-derived chemokine; MCP-1 = Monocyte chemoattractant protein -1; CRP = C-reactive protein; SAP = Serum amyloid P-component
* p-values determined with t test, all others determined with Mann-Whitney U test
^ measured in ng/mL, all others measured in pg/mL

Table 3. Cognitive performance from 31 African American Women with Parental History of AD

	Total		**Normal IL-10 (N=17)**		**Elevated IL-10 (N=14)**		**P-value^**
n (%)	31 (100)	31 (100)	17 (54.84)	17 (54.84)	14 (45.16)	14 (45.16)	
	M* ± *SD	***Mdn* (IQR)**	***M* ± *SD***	***Mdn* (IQR)**	***M* ± *SD***	***Mdn* (IQR)**	
Trails difference (B-A)*	43.6 ± 24.56	39.1 (26.26)	37.3 ± 22.72	36.2 (19.13)	51.3 ± 25.32	47.4 (25.37)	0.044
Montreal Cognitive Assessment (/30)	25.7 ± 2.71	26 (3.5)	25.9 ± 3.04	26 (4)	25.6 ± 2.34	26 (3)	0.602
Serial 3s Percent Correct (%)	90.4 ± 16.3	96.4 (14.84)	92.5 ± 11.38	100 (13.33)	87.8 ± 20.99	94.8 (15.11)	0.569
Color Word Interference Test							
Color naming scaled score (/19)	10.2 ± 3.04	11 (4.5)	10.5 ± 2.35	11 (3)	9.9 ± 3.78	10.5 (5.75)	1
Word reading scaled score (/19)	10.2 ± 2.68	11 (3)	10.5 ± 2.29	11 (3)	9.9 ± 3.15	11 (3.25)	0.762
Inhibition scaled score (/19)	10.2 ± 2.59	11 (3)	10.8 ± 1.82	11 (2)	9.6 ± 3.25	10 (4.75)	0.4
Inhibition/switching scaled score (/19)	10.5 ± 2.14	10 (3.5)	10.6 ± 1.73	10 (2)	10.3 ± 2.61	11 (4.5)	0.81
Contrast inhibition vs color naming (/19)	10 ± 2.14	10 (2.5)	10.3 ± 2.08	10 (2)	9.7 ± 2.23	10 (2.75)	0.574
Contrast inhibition/switching vs combined naming & reading (/19)	10.2 ± 2.14	10 (2)	10.1 ± 2.14	10 (2)	10.4 ± 2.21	10.5 (2.75)	0.825
Contrast inhibition/switching vs inhibition (/19)	10.3 ± 1.93	10 (2.5)	9.9 ± 1.9	10 (2)	10.7 ± 1.94	10.5 (2.75)	0.277
Inhibition total errors scaled score (/12-13)	10.7 ± 2.3	11 (2)	11.1 ± 1.54	12 (2)	10.1 ± 2.96	11 (2.75)	0.351

Inhibition/switching raw total errors	1.9 ± 2.31	1 (3)	1.7 ± 2.39	1 (2)	2.1 ± 2.28	1 (2.75)	0.46
Inhibition/switching total errors scaled score (/12-13)	10.6 ± 2.16	11 (2.5)	10.9 ± 2.25	12 (1)	10.1 ± 2.03	11 (3)	0.151
Tower of London							
Total achievement scaled score (/19)	9.7 ± 1.92	10 (2)	9.7 ± 2.08	10 (3)	9.6 ± 1.78	9 (1)	0.793
Mean first move time scaled (/17-19)	9.4 ± 2.54	10 (1.5)	9.5 ± 2.96	10 (3)	9.1 ± 1.99	10 (1)	0.807
Time per move ratio scaled (/17-18)	9.1 ± 3.3	10 (3)	8.5 ± 3.54	9 (4)	9.8 ± 2.94	10 (2.5)	0.186
Move accuracy ratio scaled (/18)	8 ± 2.71	8 (3)	7.8 ± 2.88	7 (2)	8.2 ± 2.58	8.5 (3)	0.469
Total rule violations cumulative percentile rank (/100)	58 ± 32.93	65 (75)	60.3 ± 33.64	48 (72)	55.1 ± 33.08	65 (39)	0.628
Dichotomized Variables	**n (%)**		**n (%)**		**n (%)**		
Color naming raw total errors *							1
Perfect performance	21 (67.7)		12 (70.6)		9 (64.3)		
Some errors	10 (32.3)		5 (29.4)		5 (35.7)		
Word reading raw total errors *							1
Perfect Performance	25 (80.6)		14 (82.4)		11 (78.6)		
Some errors	6 (19.4)		3 (17.6)		3 (21.4)		

Inhibition raw total errors *							0.723
Perfect Performance	15 (48.4)		9 (52.9)		6 (42.9)		
Some errors	16 (51.6)		8 (47.1)		8 (57.1)		
Color naming cumulative percentile rank (/100)							1
100 Rank	21 (67.7)		12 (70.6)		9 (64.3)		
< 100 Rank	10 (32.3)		5 (29.4)		5 (35.7)		
Word reading cumulative percentile rank (/100)							1
100 Rank	25 (80.6)		14 (82.4)		11 (78.6)		
< 100 Rank	6 (19.4)		3 (17.6)		3 (21.4)		
Rule violations per item ratio scaled (/11)							0.479
> 10	16 (51.6)		10 (58.8)		6 (42.9)		
≤ 10	15 (48.4)		7 (41.2)		8 (57.1)		

Table 3. Performance of Elevated and Normal Interleukin-10 groups of Cognitive Measures in African-American Women with Parental History of AD (n=31).

Elevated = interleukin-10 ≥ 10 pg/ml; Normal = interleukin-10, 3-10 pg/ml. All scaled and contrast measures have normative mean values of 10. Scores are scaled by age.

Mdn = median; *M* = mean; *SD* = standard deviation

*Variables that had fewer than or equal to 6 levels of frequency were dichotomized into categories, e.g., "perfect performance" vs "some errors" for the error scores, "100 % Rank" vs. "lower than 100 % rank" for the rank scores, and "Higher than 10" vs. "lower than 10" for the scaled scores. These data are presented as n (%) to represent the frequency of observation

Table 4. Nonsignificant Correlations Between IL-10 and Cognitive Tests in 31 African-American Women with Parental History of AD.

Variables	Whole Sample (N=31)	Normal IL-10 (N=17)	Elevated IL-10 (N=14)
Serial 3s Percent Correct*	-0.034 [-0.384, 0.324]	0.139 [-0.367, 0.581]	0.108 [-0.449, 0.604]
Trails difference (B-A)*	0.157 [-0.209, 0.485]	-0.387^ [-0.731, 0.116]	-0.002 [-0.532, 0.529]
Montreal Cognitive Assessment (/30)	-0.061 [-0.469, 0.344]	0.368^ [-0.209, 0.795]	-0.513^^ [-0.853, 0.000]
Color Word Interference Test			
Color naming scaled score (/19)	-0.032 [-0.411, 0.384]	-0.027 [-0.561, 0.523]	-0.070 [-0.678, 0.581]
Word reading scaled score (/19)	-0.038 [-0.425, 0.355]	0.125 [-0.392, 0.548]	-0.126 [-0.688, 0.493]
Inhibition scaled score (/19)	-0.164 [-0.489, 0.230]	0.172 [-0.300, 0.646]	-0.343^ [-0.837, 0.359]
Inhibition/switching scaled score (/19)	-0.010 [-0.412, 0.401]	0.395^ [-0.072, 0.764]	-0.342^ [-0.800, 0.246]
Contrast inhibition vs color naming (/19)	-0.099 [-0.469, 0.297]	0.061 [-0.584, 0.641]	-0.082 [-0.658, 0.495]
Contrast inhibition/switching vs combined naming & reading (/19)	0.041 [-0.348, 0.427]	0.106 [-0.475, 0.573]	-0.131 [-0.681, 0.462]
Contrast inhibition/switching vs inhibition (/19)	0.236 [-0.136, 0.552]	0.112 [-0.454, 0.598]	0.145 [-0.459, 0.725]
Color naming raw total errors	0.176 [-0.158, 0.480]	0.344^ [-0.178, 0.723]	-0.038 [-0.535, 0.469]
Color naming cumulative percentile rank (/100)	-0.195 [-0.520, 0.156]	-0.361^ [-0.724, 0.154]	0.038 [-0.468, 0.487]
Word reading raw total errors	-0.112 [-0.474, 0.265]	-0.310 [-0.632, 0.051]	-0.151 [-0.581, 0.315]
Word reading cumulative percentile rank (/100)	0.112 [-0.266, 0.440]	0.310^ [0.000, 0.652]	0.151 [-0.309, 0.578]
Inhibition raw total errors	0.132 [-0.265, 0.499]	0.036 [-0.512, 0.550]	0.072 [-0.525, 0.662]

Inhibition/switching raw total errors	-0.033 [-0.413, 0.332]	-0.301 [-0.807, 0.257]	-0.298 [-0.758, 0.222]
Inhibition total errors scaled score (/12-13)	-0.192 [-0.551, 0.228]	-0.105 [-0.627, 0.422]	-0.081 [-0.639, 0.508]
Inhibition/switching total errors scaled score (/12-13)	-0.063 [-0.437, 0.324]	0.403^ [-0.088, 0.794]	0.242 [-0.313, 0.718]
Tower of London			
Total achievement scaled score (/19)	-0.140 [-0.521, 0.236]	-0.068 [-0.474, 0.450]	-0.380 [-0.798, 0.160]
Mean first move time scaled (/17-19)	-0.005 [-0.381, 0.403]	0.174 [-0.361, 0.651]	-0.171 [0.724, 0.465]
Time per move ratio scaled (/17-18)	0.286 [-0.128, 0.621]	0.446^ [-0.058, 0.786]	-0.284 [-0.788, 0.368]
Move accuracy ratio scaled (/18)	0.094 [-0.287, 0.463]	-0.181 [-0.590, 0.319]	0.227 [-0.315, 0.651]
Total rule violations cumulative percentile rank (/100)	-0.125 [-0.495, 0.262]	0.199 [-0.277, 0.674]	-0.511^^ [-0.855, 0.126]
Rule violations per item ratio scaled (/11)	0.036 [-0.369, 0.497]	0.209 [-0.332, 0.721]	-0.330^ [-0.820, 0.255]

Table 4. Nonsignificant Correlations and 95% Confidence Intervals Between IL-10 and Cognitive Tests

Correlations were calculated within the whole sample, normal interleukin-10 group, and elevated interleukin-10 group. Confidence intervals for Spearman's rank-order correlation were calculated using the bootstrapping method with 1000 iterations.

Normal = interleukin-10, 3-10 pg/ml; Elevated = interleukin-10 ≥ 10 pg/ml

^ = moderate effect; ^^ = large effect

*Pearson's correlations were used. Spearman's rank-order correlations were used for all other variables

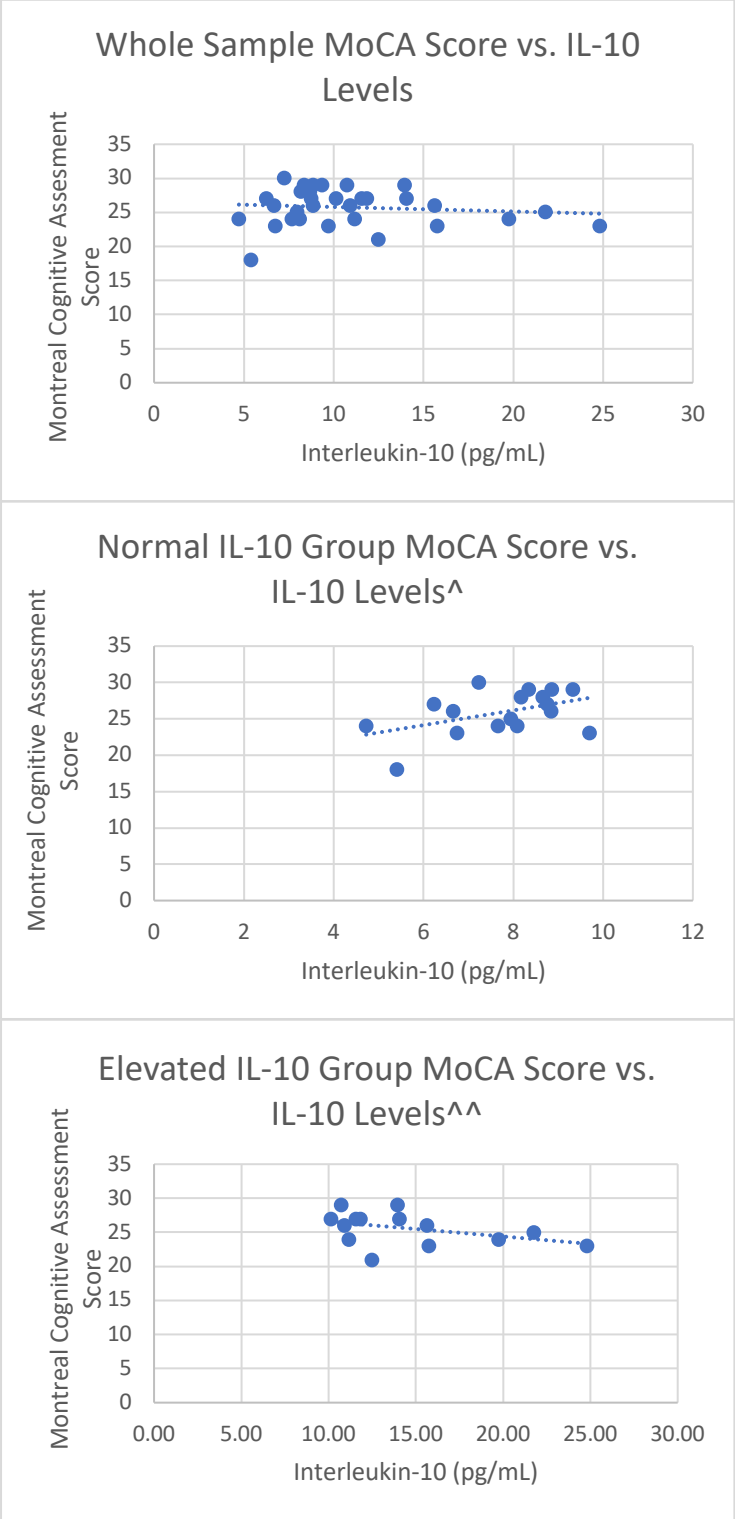

Figure 1. Nonsignificant Scatter plots of Montreal Cognitive Assessment Score and Interleukin-10 Variables in the whole sample, elevated interleukin-10 group, and normal interleukin10 group.

Elevated = interleukin-10 ≥ 10 pg/ml; Normal = interleukin-10, 3-10 pg/ml

IL= Interleukin; MoCA = Montreal Cognitive Assessment; ^ = moderate effect, ^^ = large effect

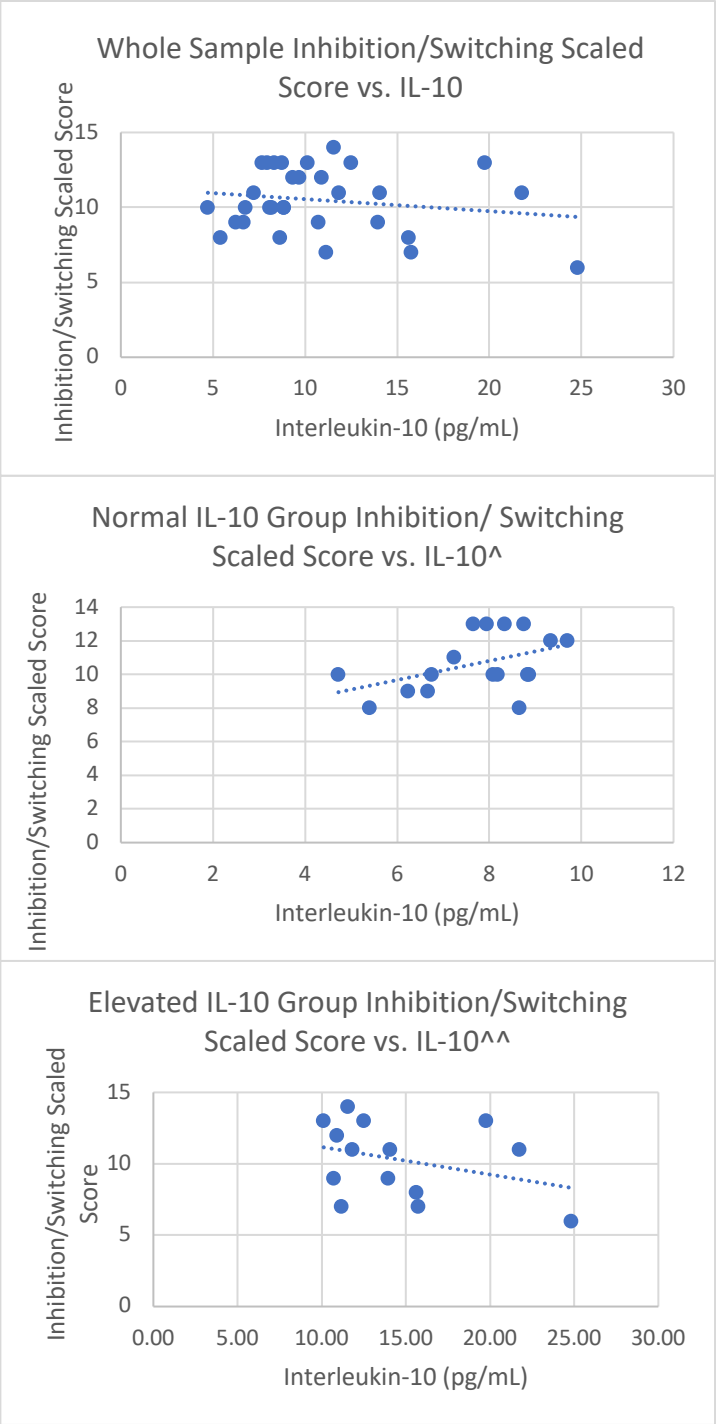

Figure 2. Nonsignificant Scatter plots of Color Word Interference Test – Inhibition/Switching Scaled Score and Interleukin-10 Variables in the whole sample, elevated interleukin-10 group, and normal interleukin-10 group.

Elevated = interleukin-10 ≥ 10 pg/ml; Normal = interleukin-10, 3-10 pg/ml; IL= Interleukin

^ = moderate effect

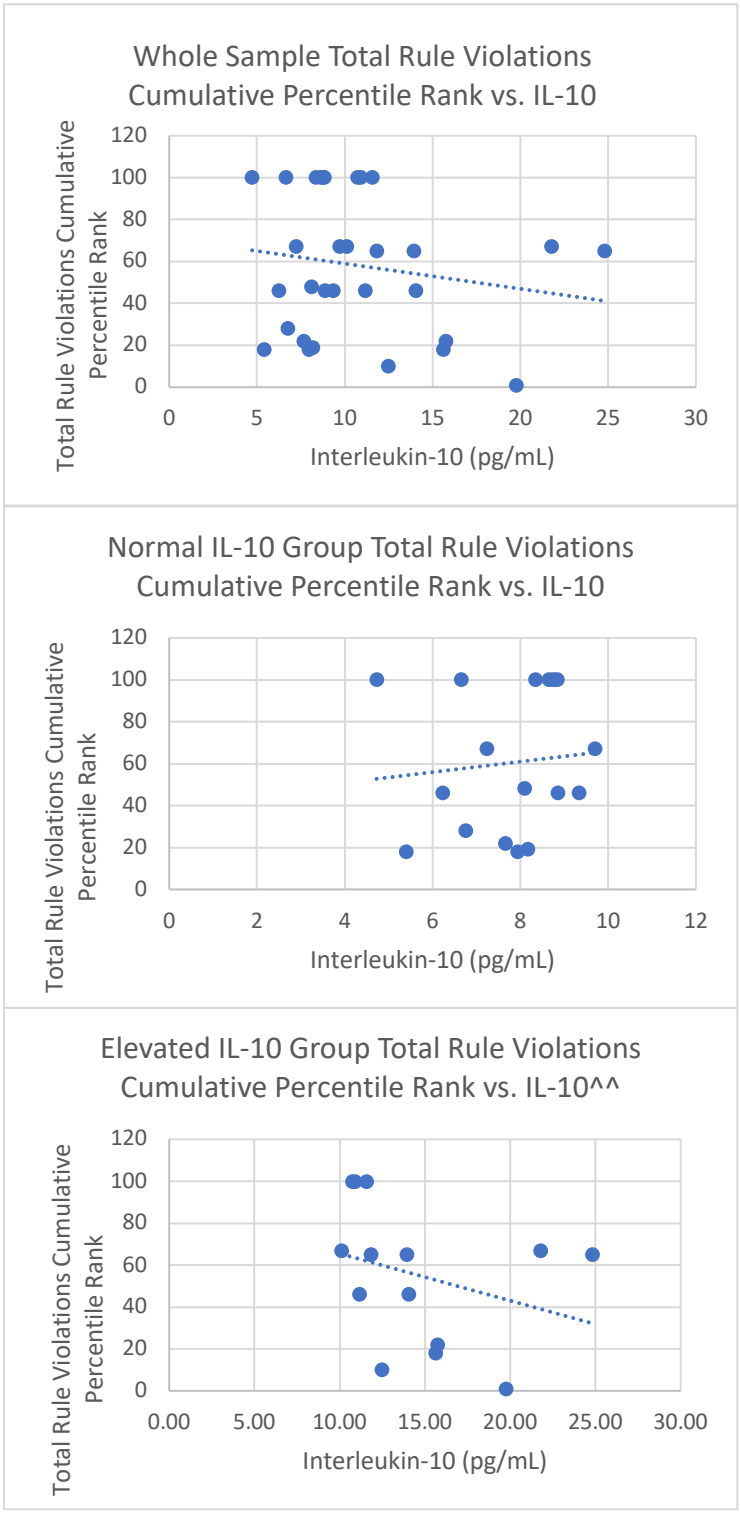

Figure 3. Nonsignificant Scatter plots of Tower of London Test – Total Rule Violations Cumulative Percentile Rank and Interleukin-10 Variables in the whole sample, elevated interleukin-10 group, and normal interleukin-10 group.

Elevated = interleukin-10 ≥ 10 pg/ml; Normal = interleukin-10, 3-10 pg/ml; IL= Interleukin

^^ = large effect

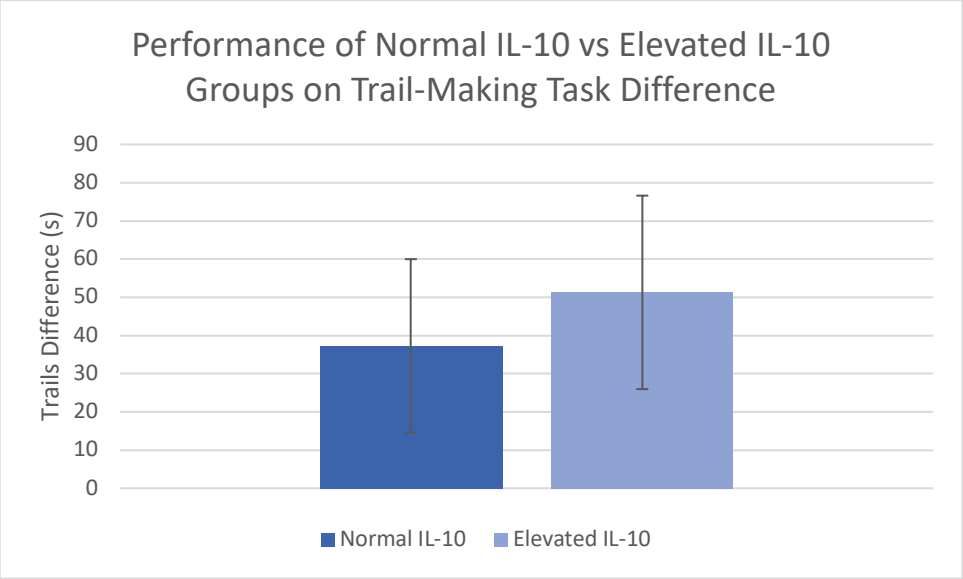

Figure 4. Trails difference performance for normal interleukin-10 group and elevated interleukin-10 group. A higher score indicates poorer performance on Trail-making Test Part B relative to Part A.

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