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# Neuroimmunoendocrine Pathology and Cognitive Function in Type 2 Diabetes

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# NEUROIMMUNOENDOCRINE PATHOLOGY AND COGNITIVE FUNCTION IN TYPE 2 DIABETES

by

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Under the Direction of Marise B. Parent, Ph.D.

## ABSTRACT

Cognitive impairment among older adults with type 2 diabetes may worsen health outcomes via negative impact on compliance with medical self-care recommendations. Results of several previous studies indicate that cognitive deficits are present in older European American adults with type 2 diabetes under some conditions, particularly related to glucose dysregulation (as evidenced by high glycated hemoglobin, i.e., HbA1c). Despite the fact African Americans are disproportionately affected by diabetes and suffer significantly greater numbers of complications and more severe complications relative to European Americans, no published studies have examined cognitive functioning among older African American adults with type 2 diabetes. Further, markers of systemic inflammation have been associated with cognitive impairment in several conditions, but this relationship has not been examined in older adults with type 2 diabetes. The purpose of the present study was to determine

whether: 1) cognitive deficits are present in older African American adults with type 2 diabetes, and whether the deficits are related to 2) glucose dysregulation and 3) systemic inflammation.

Several cognitive domains, including verbal memory and executive functions, were assessed in 71 African Americans with type 2 diabetes who ranged from 60 to 80 years of age. Exclusionary criteria included dementia, depression, neurological disease, or brain injury. Also measured were HbA1c and two markers of systemic inflammation: C-reactive protein (CRP) and interleukin-6 (IL-6). Results showed that higher HbA1c was significantly associated with poorer performance on several measures of executive function and verbal memory measures that tap executive function. Higher IL-6 was significantly associated with slower motor function and higher semantic fluency. Higher CRP was significantly associated with improved performance on measures of phonemic fluency, psychomotor speed and mental flexibility/working memory, and fine motor dexterity, but only for those with extremely high levels of CRP; when those participants were removed from the analyses, CRP was inversely related to cognitive performance.

INDEX WORDS: Type 2 diabetes, Cognition, Memory, Executive Function, Glucose, HbA1c, Inflammation, C-reactive protein, Interleukin-6, Geriatric, African Americans

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KRISTA WILD, M.A.

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# DEDICATION

This dissertation is dedicated to my mother, Diane Herblin Wild. She was the most loving and dedicated cheerleader I will ever have. She told me a few months before her untimely death that there was nothing in her life as important to her as my finishing my doctorate. I wish she had lived to see me finish, but because she was always so supportive and expressive, I am fortunate enough to know just how thrilled and proud she would have been, and exactly how that would have sounded.

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I have fierce love for several family members: My mother, Diane Wild, was an incredibly loving, funny, bright, and creative woman, and it was my honor to call her my mother. She gave me her unwavering support throughout my entire life. I am well aware of just how fortunate I have been to have known and loved her. She will be with me always. I have also been blessed with another "Mom," Barbara Burke. I adored Barbara from when I first met her when I was in my teens. I had never met anyone who made me laugh the way she did, who was simultaneously so solid and wise, and who had such an amazing aesthetic sense. My relationship with Barbara, which has always been loving and supportive, became all that much more important when my mother died. My mother would have really appreciated the way Barbara so generously continued to include me in her family, and offered her warmth, support, care, concern, nudging, and yes, wonderful cheerleading! I am greatly indebted to Barbara, and hope that I can someday offer kindnesses to her that are as meaningful and helpful as hers have been to me. My father, Gaynor Wild, is the best man I've known. Not only is he intelligent, educated, informed, and thoughtful, he is also principled, funny, and very caring. Still, there was a time when I wasn't sure we would ever have a close relationship, as we had little regular communication. Fortunately, this year he agreed to weekly phone calls, and that regular contact has made all the difference in our relationship. It is truly a wonderful thing to fully respect and admire and love someone who has known you since birth. It's even better to feel such comfort and warmth in his presence. I am very grateful for my relationship with my dad. I also thank my sister, Alison Wild, for her love and support; I want good things for both of us, always.

It has been said that friends are the family you choose. I could write a book about my friends (in no particular order) Chad Buck, Paria Banki, Amy Ross, Paula Wilbourne, Janice Bossoreale, Erin Baldwin, Steve Orey, Linda Igarashi, and David Biblin, each of whom contributed huge amounts of care, friendship, and support that enabled me to complete this project. Phillip Washington is in his own category; he helped me get through this process with large doses of humor, friendship, and support at some particularly critical times. I love all of my friends like family and am so grateful that they are in my life.

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# CHAPTER 1: INTRODUCTION

Memory impairment is the most common cognitive complaint among individuals who present for neuropsychological evaluation (Butters, Soety, & Glisky, 1998). The prospect of memory loss is cause for concern, given the potential for significant negative impact on many aspects of daily functioning and reduced quality of life (Perlmutter et al., 1987). One medical group that may be particularly impacted by cognitive impairment is older adults with type 2 diabetes, because outcomes in diabetes depend largely on the patient's consistent self-management of the condition. Given the potential for cognitive problems to interfere with attempts to self-manage medical problems and follow a physician's recommendations, cognitive deficits among older adults with diabetes could lead to further declines in health (Sinclair, Girling, & Bayer, 2000). In one longitudinal study of older adults with diabetes, even performance in the low average range on a cognitive screening measure was associated with a 20% increased risk of death 2 years later (McGuire, Ford, & Ajani, 2006).

Diabetes is a disorder in which the body does not produce or does not properly utilize insulin, which is a hormone used in the metabolism of sugars, starches, and other foods. Absence or impairment of insulin functioning in the body results in high levels of glucose in the blood and urine (hyperglycemia); these increases are paralleled by increases in brain extracellular glucose levels (McNay, McCarty, & Gold, 2001). Diabetes has more than one known etiology, the most common of which are referred to as type 1 and type 2 diabetes. Type 1 diabetes is secondary to a failure of insulin production, and is usually diagnosed prior to age 30. In contrast, type 2 diabetes results from the development of resistance to insulin, and is typically acquired in middle age or

later. Type 2 diabetes is the most common form of the disorder, representing at least 90% of the diabetes diagnoses in the U.S. (Laakso, 2003). Having diabetes increases the risk of many serious complications, including cardiovascular disease, retinopathy, neuropathy, and nephropathy. Cognitive deficits are associated with both type 1 and type 2 diabetes, although they are observed less consistently in type 1 than in type 2 diabetics (Ryan & Geckle, 2000b).

*Literature Review*

*Predictors of Cognitive Decline.* Cognitive deficits are more likely to be found among older than younger individuals with type 2 diabetes (for reviews see: Awad, Gagnon, & Messier, 2004; Ryan & Geckle, 2000b). Although cognitive deficits have been found in some studies in which middle-aged and elderly type 2 diabetics were combined into a single group (Elias, Elias, D'Agostino, Silbershatz, & Wolf, 1997; Gradman, Laws, Thompson, & Reaven, 1993; Perlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990; Vanhanen et al., 1997; Worrall, Moulton, & Briffett, 1993), studies comparing cognitive functions in middle-aged individuals with type 2 diabetes to those of age-matched controls yield no group differences (Mattlar, Falck, Rèonnemaa, & Hyyppèa, 1985; Zaslavsky, Gross, Chaves, & Machado, 1995). Such results suggest that combining older and middle-aged adults with type 2 diabetes into a single group might reduce the ability to detect group differences in cognitive performance relative to nondiabetic controls (Lowe, Tranel, Wallace, & Welty, 1994; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998). The evidence suggests that restricting the age range of a sample to older adults will maximize chances of detecting impaired cognitive functioning in adults with type 2 diabetes.

Acute and chronic glucose levels appear to be critical determinants of cognitive functioning among adults with type 2 diabetes. Experimental manipulation of acute glycemic levels reveals a significant association with cognitive performance among both middle aged and older type 2 diabetics. For instance, Greenwood, Kaplan, Hebblethwaite, and Jenkins (2003) tested a small group of middle-aged and older type 2 diabetes patients with varying levels of blood glucose, allowing them to serve as their own controls. Under hyperglycemic conditions only, a relative decline in delayed recall performance was observed on both a modified serial list learning task and an auditory-verbal paragraph recall task. In addition, older prediabetic patients with higher plasma glucose levels show changes in cognitive function similar to those seen in elderly type 2 diabetics (U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; Vanhanen et al., 1997). Furthermore, in some cases acute administration of glucose impairs memory in healthy adults (Craft, Murphy, & Wemstrom, 1994).

Chronic glucose levels also appear to be associated with cognitive deficits in type 2 diabetes. *Glycemic control* is a medical term that refers to average blood glucose levels over time in a person with diabetes. One measure of glycemic control is glycated hemoglobin. Hemoglobin is the compound in red blood cells that transports oxygen, and the most common form of hemoglobin is called hemoglobin A. Glucose binds to hemoglobin A, forming glycated hemoglobin. Glycated hemoglobin is commonly designated as HbA1c and is elevated when plasma glucose levels are high. The decomposition of glycated hemoglobin is slow and the buildup of glycated hemoglobin lasts between 1 and 4 months. HbA1c reflects mean glucose levels over the past 2 weeks to 3 months (American Diabetes Association, 2006; Garg, Sharp, & Stutts,

2006). ADA guidelines indicate that normal HbA1c is less than 6.0% (~120 mg/dL), while an HbA1c value greater than 7.0% (~150 mg/dL) represents poor glycemic control (American Diabetes Association, 2006). Several studies have shown an inverse relationship between HbA1c and verbal memory in older adults with type 2 diabetes (Gradman et al., 1993; Jagusch, Cramon, Renner, & Hepp, 1992; Perlmuter et al., 1984; Reaven et al., 1990), although a few have found no such relationship (Lowe et al., 1994; Zaslavsky et al., 1995).

Longer duration of diabetes also predicts poorer cognitive performance in both elderly and middle-aged adults with type 2 diabetes (Cosway, Strachan, Dougall, Frier, & Deary, 2001; Dey, Misra, Desai, Mahapatra, & Padma, 1997; Elias et al., 1997; Gregg et al., 2000; Grodstein, Chen, Wilson, & Manson, 2001). Longer duration of poor glycemic control may result in irreversible cognitive deficits (Awad, Gagnon, & Messier, 2004). Such duration-related cognitive changes are hypothesized to be due to prolonged hyperinsulinemia causing or contributing to the development of vascular disease. Hypoglycemic medications appear to significantly ameliorate cognitive performance regardless of the duration of diabetes (Grodstein, Chen, Wilson, & Manson, 2001), however, which suggests that glucose levels may exert a more powerful influence on cognitive functioning than the putative structural changes that occur over a prolonged course of diabetes.

Depression may also contribute to cognitive deficits among older patients with type 2 diabetes, because depression is independently associated with poorer cognitive functioning (Lezak, 1995). Increased levels of depression often co-occur with significant medical conditions (Wells, Golding, & Burnam, 1988). A recent meta-analysis

concluded that the presence of diabetes more than doubles the odds of depression (Anderson, Freedland, Clouse, & Lustman, 2001). In some studies, controlling for depression attenuated the degree of verbal memory deficits observed in older adults with type 2 diabetes (Lindeman et al., 2001; Scott et al., 1998; Tun, Perlmuter, Russo, & Nathan, 1987). In contrast, in other studies cognitive differences remained after controlling for depression (Gregg et al., 2000; Perlmuter et al., 1984; Vanhanen et al., 1997). Although it remains unclear why depression is a significant predictor in some studies and not others, it is obviously important to include this variable in any study of diabetes and cognitive function.

Type 2 diabetes is associated with an increased risk of cardiovascular disease and thus stroke and vascular dementias (Harati, 1996). The findings of one prospective study indicate that diabetics are significantly more likely than nondiabetics to develop dementia (Ott et al., 1999). In another study there were no group differences in verbal memory after excluding individuals who had been diagnosed with dementia from their study of elderly diabetic patients and matched controls (Vanhanen et al., 1999). A recent review examined a number of studies of cognitive functioning in older adults with type 2 diabetes, and concluded that a significant proportion of the variance in verbal memory could be accounted for by comorbid dementing processes (Awad, et al., 2004). Some studies have excluded older adult diabetics with dementia, however, and still found cognitive deficits (Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Vanhanen et al., 1997). These latter findings suggest that dementia is not the sole cause of cognitive deficits among older type 2 diabetics.

Diabetes is a cardiovascular risk factor. Other cardiovascular risk factors that have been associated with cognitive deficits include obesity (Gunstad, Paul, Cohen, Tate, & Gordon, 2006; Kuo et al., 2005), hypercholesterolemia (Kivipelto et al., 2001), cigarette smoking (Hill, Nilsson, Nyberg, & Backman, 2003; Kalmijn, van Boxtel, Verschuren, Jolles, & Launer, 2002), and hypertension (Kuo et al., 2005; Vicario, Martinez, Baretto, Diaz Casale, & Nicolosi, 2005; Waldstein, Brown, Maier, & Katzel, 2005). Although antihypertensive drugs appear to be protective against dementia (Forette et al., 1998), they do not improve cognitive function in older, non-demented adults with moderate hypertension (Prince, Bird, Blizard, & Mann, 1996). These latter findings suggest that hypertension can negatively impact cognition through means other than contributing to the development of vascular dementias.

Inflammation may also contribute to cognitive deficits associated with type 2 diabetes. Inflammation occurs as part of the body's nonspecific immune response. Nonspecific immunity is believed to be the body's first line of defense against infection or injury because it is faster than a specific immune response (Maier & Watkins, 1998). A specific immune response involves the development of antibodies meant to fight specific foreign substances that enter the body, and may take several hours or days to develop. In contrast, a nonspecific immune response can be seen within as little as 1 hour after a foreign substance enters the body. The nonspecific immune response includes activity by phagocytes ("eating cells") that recognize and respond quickly to foreign substances and injured tissue in the body. Responses include killing and interfering with the growth of foreign cells, and releasing proinflammatory proteins called *cytokines*. These cytokines initiate a local inflammatory response and attract other

immune cells, which can help heal the injured area (Maier & Watkins, 1998). There are also anti-inflammatory cytokines that act to dampen the immune response (O'Brien, Scott, & Dinan, 2004). In addition to their local effects, proinflammatory cytokines also produce a more global bodily response to the infection or injury called the *acute-phase response.* This involves a number of physiological adjustments including fever, and *sickness behavior*, a collection of behaviors, including reduced activity, hypersomnia or hyposomnia, and anorexia (Maier & Watkins, 1998; Reichenberg et al., 2001). It is believed that these responses to infection and injury have evolved as adaptive strategies to help the body conserve resources in order to best combat infection and heal. When the inflammatory response continues for an extended duration, however, risk of other illnesses and problems may increase.

There is a link between inflammation and diabetes. For instance, hyperglycemic crisis is associated with an increase in proinflammatory cytokines and other peripheral markers of inflammation (Stentz, Umpierrez, Cuervo, & Kitabchi, 2004). Inflammation is also associated with impaired glucose regulation (Barzilay et al., 2001; Temelkova-Kurktschiev, Henkel, Koehler, Karrei, & Hanefeld, 2002) and appears to precede and predict the development of diabetes (Barzilay et al., 2001; Duncan et al., 2003; Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Schmidt et al., 1999; Spranger et al., 2003). For instance, high levels of the inflammatory markers c-reactive protein (CRP) and interleukin-6 (IL-6) are associated with an increased risk of developing type 2 diabetes (Pradhan, Manson, Rifai, Buring, & Ridker, 2001). Importantly, increases in peripheral levels of these markers can impair the functioning of the central nervous system (Wilson, Finch, & Cohen, 2002).

Inflammation can impair cognition. High levels of the inflammatory markers CRP and IL-6 are associated with accelerated cognitive decline in healthy older adults (Engelhart et al., 2004; Teunissen et al., 2003; Weaver et al., 2002; Yaffe et al., 2003) and in older adults with metabolic syndrome (Yaffe et al., 2004). Metabolic syndrome is a cluster of several commonly occurring disorders, including impaired glucose regulation. Metabolic syndrome is diagnosed in the presence of three or more of the following: elevated waist circumference (≥ 40" in men; ≥ 35" in women), elevated serum triglycerides (≥ 150 mg/dL), reduced HDL cholesterol (< 40 mg/dL in men; < 50 mg/dL in women), hypertension (≥ 130/85 Hg), or elevated fasting glucose (≥ 100 mg/dL). Older adults with metabolic syndrome and high inflammation are at increased risk for cognitive decline, whereas those with metabolic syndrome and low inflammation are not (Yaffe et al., 2004). These latter findings in particular suggest that inflammation impacts cognition. This interpretation is supported by research in rodents showing that increases in neural levels of proinflammatory cytokines, particularly in the hippocampus, impair memory (Brennan, Beck, & Servatius, 2004; Gemma, Fister, Hudson, & Bickford, 2005; Maher, Nolan, & Lynch, 2005; Samuelsson, Jennische, Hansson, & Holmang, 2006). Moreover, decreasing brain levels of proinflammatory cytokines can reverse memory deficits (Balschun et al., 2004; Gemma et al., 2005). To date there have been no studies specifically examining the association between inflammation and cognition in type 2 diabetes.

*Diabetes and Cognition.* Older adults with type 2 diabetes appear to have impairments in verbal memory (Elias et al., 1997; Gradman et al., 1993; Greenwood et al., 2003; Lucas et al., 2005; Mooradian et al., 1988; Perlmuter et al., 1984; Perlmuter,

Tun, Sizer, McGlinchey, & Nathan, 1987; Reaven et al., 1990; Vanhanen et al., 1997). In studies examining verbal memory abilities in this population, the measures employed to assess verbal declarative memory typically consisted of standardized or experimental versions of word list learning tasks or paragraph recall tests. Findings include: 1) decrements in the number or percentage of list words recalled relative to age-matched nondiabetic controls (Mooradian et al., 1988; Perlmuter et al., 1984; Perlmuter et al., 1987; Reaven et al., 1990; Vanhanen et al., 1997), 2) increased risk of impaired immediate and delayed memory on a paragraph recall task related to duration of diagnosis (Elias, Elias, D'Agostino, Silbershatz, & Wolf, 1997), and 3) a relative decline in delayed recall performance on both a serial list-learning task and an auditory-verbal paragraph recall task under experimentally induced hyperglycemic conditions (Greenwood et al., 2003). Among middle-aged and older non-diabetic individuals with impaired glucose tolerance, there is a significant association between verbal memory deficits on a paragraph recall task and hippocampal atrophy, independent of age and score on a dementia screening measure (Convit, Wolf, Tarshish, & de Leon, 2003). This suggests a strong positive relationship between hippocampal integrity and verbal declarative memory performance in this population.

Although the primary cognitive deficit among older adults with type 2 diabetes is typically purported to involve verbal declarative memory, there are compelling reasons to suspect that deficits in executive functioning may play a more critical role. Executive functions include the ability to think abstractly and to plan, initiate, sequence, monitor, and inhibit complex, goal-directed behavior (DSM-IV; American Psychiatric Association, 1994). Relative to other cognitive abilities, executive functions appear to be

disproportionately affected by cardiovascular risk factors and disease. Executive dysfunction has been linked to hypertension in older adults (Vicario, Martinez, Baretto, Diaz Casale, & Nicolosi, 2005), and is associated with acute elevations in blood pressure in otherwise healthy older adults (Kuo et al., 2004). Furthermore, in a study of older adult African Americans, a summary cardiovascular risk score was associated with impairment in executive functions, but not in other cognitive skills, such as episodic memory or visuospatial function (Pugh, Kiely, Milberg, & Lipsitz, 2003). Given that diabetes is a cardiovascular risk factor, in the absence of any other information it would be reasonable to hypothesize that the primary cognitive deficit associated with type 2 diabetes is executive.

It is possible that, in some instances, a result that is interpreted as showing a verbal memory deficit actually reflects a problem with executive functions. The most common ways to assess verbal learning and memory are paragraph recall tasks such as the Logical Memory subtest from the Wechsler Memory Scale, and word list learning tasks like the California Verbal Learning Test (CVLT). Initial correlational research indicated that the two tests were highly related (Delis, Cullum, Butters, & Cairns, 1988), and might be used interchangeably. Subsequent studies, however, have revealed critical differences between the two tasks. For example, compared to healthy controls, adults with executive dysfunction are impaired on CVLT-II but not on Logical Memory (Brooks, Weaver, & Scialfa, 2006; Tremont, Halpert, Javorsky, & Stern, 2000). In fact, the CVLT measures a combination of verbal learning and memory, conceptual ability, and strategic organization (Lezak, 1995), and requires intact executive functions for adequate performance. A recent review study (Awad et al., 2004) revealed that adults

with type 2 diabetes are more commonly impaired on “noncontextual” word list learning tasks, which require examinees to structure the information, than on paragraph recall/contextual tasks, in which the information is provided to examinees in a structured format. Thus, interpreting poor performance on the CVLT as being indicative of a verbal memory deficit could be misleading.

The CVLT consists of a 16-item word list which is read aloud several times, followed each time by a free recall trial and, after 20 minutes, a delayed free recall trial. Each of the 16 words on the list belongs to one of four semantic categories (e.g., fruits, herbs and spices, articles of clothing, and tools). The ability to detect and make use of categories to facilitate performance is a common feature of tasks designed to measure the integrity of executive functions. Optimal CVLT performance is obtained when the semantic categories of the words are noticed and used spontaneously to organize list words during encoding and to facilitate later recall (Alexander, Stuss, & Fansabedian, 2003; Gershberg & Shimamura, 1995). A failure of subjective organization as a learning and recall strategy may result in significant reductions in the number or percentage of list words freely recalled. Previous studies of older adults with type 2 diabetes using word list learning tasks typically reported only the total number or percentage of words recalled across all learning trials (Perlmuter et al., 1987; Reaven et al., 1990). When such data are presented in isolation, the source of the cognitive deficit is ambiguous, and could reflect deficits other than verbal memory. Consequently, it is impossible to determine whether an executive deficit contributed to a poor performance on this measure without examining other CVLT performance indicators, such as subjective strategy use. The semantic clustering score provides a measure of one

particularly effective type of strategy an examinee could employ in order to facilitate the encoding and subsequent retrieval of list words. The CVLT-II, a revised version of the CVLT released in 2000, includes several changes, including a larger normative sample, improved word lists, and revised scoring methods for the semantic clustering indices to adjust for chance levels of semantic clustering during word recall.

The relationship between type 2 diabetes and executive functions is inconsistent. Poor performance on measures of executive function has been found in some studies of adults with type 2 diabetes (Elias et al., 1997; Gregg et al., 2000; Perlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990; Vanhanen et al., 1999), but not in others (Gradman et al., 1993; Greenwood et al., 2003; U'Ren et al., 1990). Group differences between adults with type 2 diabetes and controls have been observed on several different measures of executive function, including: Trail Making Test, part B (Gregg et al., 2000; Reaven et al., 1990; Vanhanen et al., 1999), Stroop Interference (Ryan & Geckle, 2000a), Phonemic Fluency (Hewer, Mussell, Rist, Kulzer, & Bergis, 2003; Lowe et al., 1994), Semantic Fluency (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004), and Wisconsin Card Sorting Test (WCST; Reaven, Thompson, Nahum, & Haskins, 1990). Symbol Digit Modalities Test (SDMT) is a measure of processing speed and working memory. SDMT (written version) did not differentiate adults with and without diabetes (U'Ren, Riddle, Lezak, & Bennington-Davis, 1990). Given that adults with type 2 diabetes purportedly have verbal memory deficits, any difficulties on SDMT may become more apparent when the oral version is administered.

Using neuropsychological tests to isolate distinct executive deficits can be difficult because all neuropsychological tests categorized as executive function

measures require multiple executive functions (Daniels, Toth, & Jacoby, 2006). In addition, the executive functions attributed to various measures vary across authors and studies, and may change depending on the age groups and participant populations in a given study. Thus, different outcomes on these tests do not clarify which executive functions might be impaired by diabetes. Nonetheless, aside from WCST, a common thread that may underlie the majority of executive tasks on which group differences between adults with and without type 2 diabetes have been detected is working memory. In fact, there is evidence linking CVLT performance and working memory. In one study, two CVLT factors—general verbal learning and working memory—along with Trails B and Digit Span were significantly correlated with a canonical variable that accounted for 29% of the variance in the data (Vanderploeg, Schinka, & Retzlaff, 1994). In PET studies of healthy participants engaged in encoding word lists with varying demands for semantic organization, use of semantic organization strategies was associated with increased regional cerebral blood flow (rCBF) in dorsolateral prefrontal cortex (DLPFC; Fletcher, Shallice, & Dolan, 1998; Savage et al., 2001). Several imaging studies indicate that DLPFC activation is associated with conditions that require monitoring, manipulating and/or updating the contents of working memory (Blumenfeld & Ranganath, 2006; Gerton et al., 2004; Staresina & Davachi, 2006; Volle et al., 2005).

*Diabetes and African Americans.* Surprisingly, there do not appear to be any comprehensive studies of cognitive function in African-American elders with type 2 diabetes. Compared to Americans of European descent, African Americans are disproportionately affected with type 2 diabetes (Brancati, Kao, Folsom, Watson, & Szklo, 2000; Harris et al., 1998; Robbins, Vaccarino, Zhang, & Kasl, 2000). Failure to

take medication because of forgetting to do so is a significant predictor of poor glycemic control in African Americans (Hill-Briggs et al., 2005), indicating that cognitive deficits may have a strong impact on health in this population. Importantly, the effects of type 2 diabetes on cognition may be moderated by ethnicity. For example, although cognitive deficits are found in older adult European Americans with type 2 diabetes, none were found in elderly Native Americans with type 2 diabetes once the effects of depression were removed (Lowe, Tranel, Wallace, & Welty, 1994). Contrary to expectations based on studies of older adult Caucasians, one study of 43 African American participants aged 43-82 years (*M* = 59) showed that higher levels of HbA1c predicted *improved* performance on a measure of attention, and was marginally associated with better executive functions (Izquierdo-Porrera & Waldstein, 2002). The fact that middle aged participants were included and that only 19% of the participants (N = 9) had self-reported diabetes diagnoses, however, make it difficult to draw any strong conclusions from this study about the relationship between cognition and diabetes in African Americans. A study employing a larger sample of older adult African Americans with physician-confirmed diagnoses of type 2 diabetes and which excludes middle aged participants would help to clarify the relationship between cognition and diabetes in this population.

*Present Study.* The purpose of the present study was to determine whether: 1) cognitive deficits are present in older African American adults with type 2 diabetes, and whether they are related to 2) glucose dysregulation and 3) inflammation. An additional aim of the present study was to obtain a more comprehensive analysis of executive functions in older adults with Type 2 diabetes, and to determine whether CVLT-II

subjective organization in the form of semantic clustering is impaired in this population. To address these objectives, this study compared scores of older adults with type 2 diabetes with published normative data on measures of cognitive function that included multiple measures of verbal declarative memory and of executive function. Subsequently, participants' cognitive test scores, HbA1c levels (an indicator of glucose regulation), and levels of CRP and IL-6 (two markers of inflammation) were analyzed statistically in order to identify any relationships between cognitive performance, glucose regulation, and inflammation. CRP and IL-6 were selected as the two markers of inflammation because of extensive evidence linking these markers with cognitive deficits (Engelhart et al., 2004; Schmidt et al., 2002; Samuelsson et al., 2006; Teunissen et al., 2003; Weaver et al., 2002; Yaffe et al., 2004; Yaffe et al., 2003). Specifically, higher levels of IL-6 and CRP have been associated with increased rates of cognitive decline (Yaffe et al., 2003) and dementia (Engelhart et al., 2004; Schmidt et al., 2002) in healthy older adults, and in older adults with metabolic syndrome (Dik et al., 2007; Yaffe et al., 2004). Higher baseline plasma IL-6 in a large sample of nondisabled elderly people was associated with an increased risk of cognitive decline at a 7-year follow-up (Weaver et al., 2002). In a sample of healthy elderly people, higher CRP levels at baseline were associated with a decline in performance on a word list learning task over a 6-year follow-up period (Teunissen et al., 2003).

*Hypotheses and Predictions.* **The first hypothesis was that older African-American adults with uncontrolled type 2 diabetes would have cognitive deficits, particularly in verbal declarative memory and executive functions.** It was predicted that participants with type 2 diabetes would score significantly below the mean for

healthy controls in published normative data on CVLT-II measures of immediate and delayed recall and semantic clustering. In addition, it was expected that participants with type 2 diabetes would perform significantly below average according to published norms for healthy controls on measures of executive function tapping working memory, including: Trail Making Test Part B, Stroop Color-Word, Phonemic and Semantic Fluency, and Symbol Digit Modalities Test. It was also predicted that participants with type 2 diabetes would perform in the normal range according to published normative data for healthy control participants on measures of memory that are less dependent on executive functions (i.e., paragraph recall), and on other cognitive measures (e.g., simple attention, visuospatial judgment, fine motor dexterity).

**The second and third hypotheses were that cognitive deficits would be significantly predicted by glucose dysregulation (high HbA1c) and inflammation (elevated levels of the pro-inflammatory markers CRP and IL-6).** It was predicted that participants with 1) high HbA1c and/or 2) high CRP and IL-6 levels would score significantly lower than participants with normal levels of HbA1c and/or normal CRP and IL-6 levels on CVLT-II immediate and delayed recall and semantic clustering, and on measures of executive function, including: Trail Making Test Part B, Stroop Color-Word, Phonemic and Semantic Fluency, and Symbol Digit Modalities Test. It was also predicted that HbA1c and the inflammation markers would not predict performance on measures of memory that are less dependent on executive functions (i.e., paragraph recall), or on other cognitive measures (e.g., simple attention, visuospatial judgment, fine motor dexterity).

# CHAPTER 2: METHOD

*Participants*

Potential participants were identified via a database of patient records at the Diabetes Clinic at Grady Memorial Hospital. Individuals with a diagnosis of type 2 diabetes who met other demographic criteria for the study were contacted by phone and invited to participate in the study. Those individuals who expressed interest in the study were asked a series of screening questions in order to verify their suitability for the study. Exclusionary criteria included: 1) history of head injury or major neurological disorder (including cerebral vascular accident and recent myocardial infarction), 2) current clinically significant levels of depression or anxiety, or history of other major psychiatric disorder, 3) significant and uncorrected sensory deficits (e.g., vision, hearing), and 3) current or previous history of substance abuse, including alcohol. Alcohol abuse was defined as two or more drinks per day in women, and three or more drinks per day in men. In addition, given that estrogen replacement therapy in women affects cognition in differing ways depending on factors such as timing of therapy initiation (MacLennan et al., 2006) and comorbid medical conditions (Grady et al., 2002; MacLennan et al., 2006), female participants recruited for the study were not on estrogen replacement therapy. Individuals who met criteria and agreed to participate in the study were instructed that on the day of their appointment for testing they were to take their normally prescribed medications and to bring along their glasses and/or hearing aids.

Of the 85 participants enrolled in the study, 14 participants were excluded from or discontinued testing. Reasons for being excluded from testing included: Impaired

performance on measures screening for dementia (*n* = 3) or depression (*n* = 4), reported history of excluded neurological conditions (*n* = 4), significant sensory impairments (*n* = 3). In addition, one participant discontinued testing for undisclosed reasons. Patients excluded from the study based on dementia and depression screenings were referred for psychiatric or neurological examinations. The remaining 71 participants were African American adults (62 females and 9 males) who ranged in age from 60 to 80 years (*M* = 67.01; *SD* = 5.0).

*Measures*

Medical variables that were measured included weight, blood pressure, abdominal circumference, and serum levels of HbA1c, CRP, and IL-6. The neuropsychological tests that were administered are commonly used, standardized measures of intellectual and cognitive functioning. A listing and description of the measures follows. Although several of the tests tap more than one cognitive domain, in the following list each test was assigned to a single cognitive domain.

*Mood Assessment*. The Geriatric Depression Scale (GDS; Yesavage et al., 1982) consists of 30 statements about the examinee's current/recent feelings and behaviors which are read aloud to the participant. The examinee responds with "yes" or "no" to each statement.

*Cognitive Screening.* The Modified Mini-Mental State Examination (3MS; Teng & Chui, 1987) is a screening test for memory problems and dementia. This measure probes abilities across a number of areas, including orientation (e.g., to self, time, date, place), memory, attention and calculation, spoken and written language, and the ability to copy and remember named objects. Clock Drawing (Spreen & Strauss, 1998) is a

screening test that assesses cognitive or visuospatial impairment. The examinee draws a clock, including the numbers and the hands at a time designated by the examiner.

*Estimated IQ.* The North American Adult Reading Test (NAART; Blair & Spreen, 1989) is a reading test consisting of 61 irregularly spelled words that examinees read aloud. Accuracy of pronunciation of list words is used to estimate verbal IQ. NAART and years of education can be used in a formula to predict a WAIS-R Vocabulary score (Uttl, 2002).

*Attention.* The Digit Span (DS) subtest from the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997) is a brief test of simple auditory attention and auditory-verbal working memory. The examiner reads aloud increasingly long series of digits, and the examinee attempts to repeat back the digit strings in the same order (Digits Forward), or in reversed order (Digits Backward).

*Memory.* During the Logical Memory (LM) subtest of the WMS-III, the examiner reads aloud two short stories. After each story, the examinee attempts to recall verbally as much of the story as possible. Following a distraction-filled delay, the examinee verbally recalls the stories again. The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) assesses several aspects of verbal learning, organization, and memory. Examinees are read a list of words and asked to recall them in a series of trials, and then again following a distraction-filled delay. Recognition is also probed.

*Executive Functions.* The Trail Making Test (TMT; Reitan & Wolfson, 1985) is a timed measure of motor speed, visual attention, and working memory. The examinee draws lines on a page connecting consecutive series of numbers (Trails A) or alternating numbers and letters (Trails B). The Stroop Color and Word Test (SCWT;

Golden, 1978) is a timed measure of attention, mental speed, and mental control. The examinee names the colors of squares printed on a page, reads words printed on a page (all are names of colors), and then names the color of the ink in which some words (which name different colors) are printed. The Symbol Digit Modalities Test (SDMT; Smith, 1982) is a measure of mental speed, motor speed, visual scanning, and mental flexibility/working memory. The examinee pairs specific numbers with given geometric figures under timed conditions. The Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1994; Spreen & Strauss, 1998) is a set of tasks measuring speed and fluency of verbal thought processes. Phonemic fluency tasks assess a person's ability to rapidly produce words beginning with a given letter. Semantic fluency tasks measure a person's ability to rapidly produce words fitting into a particular semantic category (e.g., animals).

*Language.* The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001) assesses object naming ability through spontaneous responses and the need for various types of cueing. The examinee views a series of 60 drawings of objects, and names each item aloud within a 20-second time frame.

*Visuospatial Skill*. Judgment of Line Orientation (JOLO; Benton, Sivan, Hamsher, Varney, & Spreen, 1994) is a measure of visuospatial judgment. Initially the examinee is presented with an array of numbered lines arranged at varying angles. Subsequently the examinee must correctly identify by number the orientations of a series of line pairs presented in isolation from the array.

*Motor Skill*. The Grooved Pegboard Test (GPT; Lafayette Instrument Company, 1997) is a timed measure of fine motor coordination consisting of a pegboard with 25

randomly positioned slots. Pegs with a ridge along one side must be rotated to match the hole before they can be inserted.

*Procedure*

Testing took place in the Outpatient Research Unit of Grady Diabetes Clinic at Grady Memorial Hospital. After the study was fully described and consent was obtained, participants were screened for depression and dementia. Participants who passed the screenings underwent a battery of neuropsychological testing consisting of a series of paper and pencil tests, which lasted approximately 2 hours. Following neuropsychological testing, several medical variables were measured, including blood pressure, abdominal circumference, and weight. Body Mass Index (BMI) was calculated using the weight measurement obtained during the appointment and participants' self-reported height. Finally, a phlebotomist took a blood sample from the participant's arm in order to measure serum levels of CRP, IL-6, and HbA1c. Participants were paid $30 for each complete session of neuropsychological testing. During the informed consent process, participants were informed that they had a right to discontinue participation in the study at any time. They were also informed that participants who elected to stop participating in the study would receive a prorated amount of compensation at the rate of $10 per hour of completed testing. Prior to the initiation of the study, IRB approval was obtained from both Georgia State University and Emory University.

*Data Analyses*

All data were entered into SPSS, checked for accuracy, and screened for outliers and violations of the assumptions of relevant statistical tests. One variable (IL-6) was

log transformed to reduce skewness. Descriptive statistics, including means and standard deviations, were compiled for all demographic, biomedical, and neuropsychological measures. As constraints on participant recruitment did not permit the recruitment of a control group, scores from measures of cognitive functioning were compared with demographically appropriate normative data for the general population, if available, and converted into standard scores. Scores from several neuropsychological measures were then categorized to indicate the percentages of participants falling into specified z-score ranges.

Mayo's Older African American Normative Studies (MOAANS; Lucas et al., 2005) was the source of ethnically appropriate normative data grouped by age and education level for the following measures: Stroop Test, Trail Making Test, Phonemic Fluency – CFL, Semantic Fluency – Animal Naming, and Boston Naming Test. Normative data for Grooved Pegboard and Phonemic Fluency – FAS was grouped by ethnicity, sex, age, and education (Heaton, Miller, Taylor, & Grant, 2004). Normative data for the CVLT-II was obtained via the CVLT-II scoring software, which controls for age and sex only; normative sample cell sizes were too small to adequately stratify the sample across education levels (Delis et al., 2000). Normative data for WAIS-III Digit Span and WMS-III Logical Memory were obtained from the WAIS-III/WMS-III/WIAT-III computer scoring software program (The Psychological Corporation, 2001), which includes demographic corrections for ethnicity, sex, age, and, education level. Normative data for SDMT were obtained from the test manual (Smith, 1982), and corrects for age (to 78 years) and education (12 years or less or 13 years or more). No normative data were available for the following measures: Semantic Fluency – Boys Names, and a 15-item version of

Judgment of Line Orientation in which the odd items from either form H or form V were administered.

Predictions about the association between HbA1c, IL-6, and CRP and cognition were tested using a series of hierarchical multiple regression analyses. Criterion variables were select raw scores from the administered neuropsychological measures. Due to their covariance with the criterion variables, age and reading level (NAART) were controlled for in all analyses by regressing these variables on the criterion variable at the first step. Age and education are two of the strongest predictors of performance scores on measures of neuropsychological functioning. In the current study, reading level was chosen as a proxy for education level in analyses because studies have shown that: 1) among African American elders, reading level falls significantly below that predicted by self-reported education level (O'Bryant et al., 2007), and 2) reading level appears to be related to aspects of the educational experience that are important for performance on cognitive tests across several domains (Manly, 2005). Predictor variables were added to all regression equations in the following order: 1) age and NAART score, 2) HbA1c, and 3) IL-6, and CRP. Given that glucose regulation is a relatively robust predictor of cognitive performance across studies, HbA1c was entered alone in the second block, and the more exploratory predictor variables measuring inflammation (IL-6 and CRP) were entered together in the third step. Sets of hierarchical multiple regression analyses will be presented grouping test scores from measures of 1) executive function, and 2) verbal memory. A third set of hierarchical multiple regression analyses consisted of scores from cognitive measures on which no significant effects of the independent variables were predicted.

# CHAPTER 3: RESULTS

*Descriptive Statistics*

Table 1 shows frequencies, means, standard deviations, and variances for demographic, biomedical, and psychological variables. Participants were predominantly female (87.3%) and had 11.3 ± 2.6 years of education (5 to 18 years). Time since diagnosis of type 2 diabetes was obtained from the patient database, and was measured in years. Duration of diabetes in this sample ranged from 1 to 47 years (*M* = 14.84; *S.D.* = 9.28). Means for BMI and abdominal circumference were well above recommended limits. Adults are considered overweight with a BMI between 25 and 30, and are considered obese with a BMI over 30. According to those guidelines, the BMI data for this sample indicates that 7.4% were of normal weight, 22.1% were overweight, and 70.6% were obese. National Heart Lung and Blood Institute guidelines state that abdominal circumference has some predictive value of disease beyond that of BMI, but not when BMI is over 35. In this sample only one participant had an abdominal circumference under 35. The target blood pressure range for people with diabetes is <130/80 mmHg (American Diabetes Association, 2003). In this sample, the systolic goal was met by 31.9%, and the combined systolic/diastolic goal was met by 20.3% of individuals.

American Diabetes Association standards of care indicate a target HbA1c of < 7% for people with diabetes (American Diabetes Association, 2006), a goal met by 27% of the sample in which it was measured (*n* = 63). Applying the cardiovascular risk level cutpoints for high sensitivity CRP (hs-CRP) test results (Pearson et al., 2003) to the sample data reveals that 28.2% fall in the range corresponding to low to average risk (<

1.0 mg/L to 3.0 mg/L), 40.8% are in the high risk range (> 3.0 mg/L to 10 mg/L), and 31% have markedly high hs-CRP levels (> 10 mg/L). Reference ranges for IL-6 could not be obtained.

Table 1
*Demographic, biomedical, and psychological screening characteristics of the sample.*

| Variable | Frequency | Percentage | | |
|---|---|---|---|---|
| Sex | | | | |
| Female | 62 | 87.3 | | |
| Male | 9 | 12.7 | | |
| Handedness | | | | |
| Right | 67 | 94.4 | | |
| Left | 4 | 5.6 | | |
| | Mean | S.D. | Minimum | Maximum |
| Age (yrs) | 67.06 | 5.00 | 60 | 80 |
| Education (yrs) | 11.30 | 2.57 | 5 | 18 |
| Duration of diabetes (yrs) | 14.84 | 9.28 | 1 | 47 |
| BMI | 33.52 | 6.28 | 20.60 | 49.70 |
| Abdominal circumference (in) | 46.57 | 5.32 | 34 | 59 |
| BP Systolic | 137.67 | 21.83 | 100 | 220 |
| BP Diastolic | 83.88 | 13.82 | 50 | 120 |
| HbA1c | 8.17 | 1.97 | 5.60 | 14.60 |
| Interleukin-6 (pg/mL) | 4.01 | 5.94 | .58 | 40.00 |
| C-reactive protein (mg/L) | 8.83 | 8.65 | .08 | 46.41 |
| GDS | 4.20 | 3.74 | 0 | 18 |
| 3MS | 87.07 | 6.15 | 71 | 100 |
| NAART | 12.40 | 8.59 | 1 | 35 |
| Predicted WAIS-R Vocabulary Scaled Score | 8.38 | 1.77 | 5.25 | 13 |

According to the cutoff scores issued for the 30-item form of the Geriatric Depression Scale (GDS), normal range is 0 to 9, mild depression is 10 to 19, and severe depression is 20 to 30 (Yesavage et al., 1982). By these criteria, 88.7% of participants in the sample fell in the normal range, and 11.3% fell in the mildly

depressed range. Participants with a GDS score higher than 19 were excluded from the study.

A cutoff score of 70 on the Modified Mini-Mental State Examination (3MS) was used to exclude participants from the study. The 3MS scores of the sample ranged from 71 to 100 (*M* = 87.07; *S.D.* = 6.15). 3MS normative data for older adult African Americans is available (Brown, Schinka, Mortimer, & Graves, 2003) stratifying data by sex, age (60-71 or 73-84), and education (< 12, 12, or > 12 years). Given that cell sizes were small at the two higher education ranges (as low as *n* = 2), data from the present sample were compared to normative data using only sex and age range. Using these criteria, 91.6% of the sample (*n* = 65) had a 3MS score within 1.5 standard deviations of the age and sex appropriate normative data. Only 4.2% of the sample (*n* = 3) scored more than 2 standard deviations above the published norms; those scores were above our cutoff, at 74 and 75.

The North American Adult Reading Test (NAART) scores for the sample ranged from 1 to 35 (*M* = 12.40; *S.D.* = 8.59). NAART performance is reportedly correlated with education and social class, but not with age, gender, or ethnicity (Strauss, Sherman, & Spreen, 2006). Using NAART scores predicted based solely on age and education (Uttl, 2002) produced predicted scores that were an average of 19.45 raw score points higher than the observed scores from this sample of participants. Thus, it may be that social class, which is not accounted for by this prediction equation, is a robust predictor of NAART performance in this sample. Using an equation designed to predict WAIS-R Vocabulary subtest scores based on NAART score and years of education (Uttl, 2002) yielded scaled scores ranging from 5.25 to 13 (*M* = 8.38; *S.D.* = 1.77).

Descriptive statistics for neuropsychological outcome measures are shown in Table 2. Examination of the standardized scores reveals that mean scores for most neuropsychological tests fell in the average range or higher. Exceptions included: 1) SDMT Written and SDMT Oral, which fell in the mildly impaired range, 2) CVLT-II Short Delay Free Recall, Long Delay Free Recall, and Long Delay Semantic Clustering, all of which were in the low average range, and 3) Grooved Pegboard, which was in the low average range for both hands. Mean scores for a sample with such a wide range of ages and reading levels, however, may fail to adequately characterize performance levels. To address this concern, Table 3 displays the percentage of participants falling into specific z-score ranges for the neuropsychological measures in the study purported to tap executive functions. Examination of this table reveals that across tests, the percentage of participants falling more than one standard deviation below the norm ranged from 17.6 to 67.6 percent. Based on the percentage of scores falling at least one standard deviation below the mean on this group of measures, participants in this sample appear to have performed best on Semantic Fluency (on which only 2.8% of the sample more than 1 S.D. below the mean score), followed by Phonemic Fluency (21.3% averaged across CFL and FAS), Stroop Color-Word (27.4%), Trail Making Test Part B (39.4%), SDMT Written (62.0 %), and SDMT Oral (67.6%). Table 4 displays the percentage of participants falling into specific z-score ranges for relevant indices on the administered measures of verbal memory. The distributions across the z-score range in this table indicates that the participants in this sample performed best on Logical Memory Immediate and Delayed Recall (both of which were associated with 11.3% of the sample scoring more than 1 S.D. below the norm), followed by scores from the

Table 2
*Descriptive statistics for neuropsychological outcome measures.*

| Measure | *n* | Mean | S.D. | Standardized Score | S.D. |
|---|---|---|---|---|---|
| Stroop Color-Word | 69 | 21.06 | 10.61 | 9.57 | 3.45 |
| Trail Making Test Part B | 71 | 209.28 | 87.44 | 8.37 | 3.45 |
| Semantic Fluency | 71 | 14.65 | 4.17 | -- | -- |
| Animal Naming | 36 | 14.83 | 3.29 | 11.12 | 2.54 |
| Boys Names | 35 | 14.46 | 4.96 | -- | -- |
| Phonemic Fluency | 71 | 26.38 | 11.08 | -- | -- |
| CFL | 36 | 26.11 | 11.50 | 8.90 | 3.04 |
| FAS | 35 | 26.66 | 10.79 | 48.41 | 9.26 |
| Symbol Digit Modalities Test | | | | | |
| Written | 71 | 26.21 | 12.03 | -1.39 | 1.34 |
| Oral | 71 | 30.80 | 12.62 | -1.49 | 1.22 |
| WAIS-III Digit Span Total | 70 | 12.31 | 3.13 | 46.49 | 6.93 |
| Digits Forward | 70 | 7.96 | 1.98 | -- | -- |
| Digits Backward | 70 | 4.36 | 1.68 | -- | -- |
| CVLT-II | | | | | |
| Short Delay Free Recall | 71 | 6.77 | 2.90 | -.85 | .94 |
| Short Delay Semantic Clustering | 71 | .79 | 1.39 | -.63 | 1.01 |
| Long Delay Free Recall | 71 | 8.61 | 3.17 | -.96 | .78 |
| Long Delay Semantic Clustering | 71 | .96 | 1.40 | -.72 | .61 |
| WMS-III Logical Memory | | | | | |
| Immediate Recall | 71 | 32.45 | 9.85 | 53.31 | 12.36 |
| Delayed Recall | 71 | 18.39 | 7.12 | 56.58 | 12.96 |
| Grooved Pegboard | | | | | |
| Dominant | 70 | 130.40 | 55.42 | 42.26 | 8.95 |
| Non-dominant | 70 | 161.03 | 66.88 | 40.91 | 10.51 |
| Boston Naming Test | 71 | 39.94 | 9.44 | 9.10 | 2.92 |
| Judgment of Line Orientation 15-item | 70 | 7.91 | 3.53 | -- | -- |

Table 3
*Percentage of participants within specified z-score ranges on executive function measures.*

| Standard deviation from the mean | Stroop CW | Trails B | Semantic Fluency - Animals | Phonemic Fluency CFL | Phonemic Fluency FAS | SDMT Written | SDMT Oral |
|---|---|---|---|---|---|---|---|
| +3.0 to +2.0 | 4.3 | 1.4 | 5.6 | 0.0 | 2.9 | 0.0 | 0.0 |
| +1.99 to +1.0 | 8.7 | 11.3 | 19.4 | 11.1 | 5.9 | 2.8 | 1.4 |
| +.99 to 0 | 42.0 | 28.2 | 50.0 | 33.3 | 32.4 | 12.7 | 7.0 |
| –.01 to –1.0 | 27.5 | 19.7 | 22.2 | 30.6 | 41.2 | 22.5 | 23.9 |
| –1.01 to –2.0 | 14.5 | 35.2 | 2.8 | 22.2 | 17.6 | 26.8 | 36.6 |
| –2.01 to –3.0 | 2.9 | 4.2 | 0.0 | 2.8 | 0.0 | 35.2 | 31.0 |

Table 4
*Percentages of participants within specified z-score ranges on verbal memory measures.*

| Standard deviation from the mean | CVLT-II Short Delay Free Recall | CVLT-II SDFR Semantic Clustering | CVLT-II Long Delay Free Recall | CVLT-II LDFR Semantic Clustering | Logical Memory Immediate Recall | Logical Memory Delayed Recall |
|---|---|---|---|---|---|---|
| +3.0 to +2.0 | 0.0 | 0.0 | 1.4 | 0.0 | 7.0 | 16.9 |
| +1.99 to +1.0 | 7.0 | 4.2 | 1.4 | 4.2 | 28.2 | 28.2 |
| +.99 to 0 | 22.5 | 22.5 | 23.9 | 11.3 | 29.6 | 29.6 |
| –.01 to –1.0 | 35.2 | 49.3 | 40.8 | 70.4 | 23.9 | 14.1 |
| –1.01 to –2.0 | 29.6 | 23.9 | 25.4 | 14.1 | 8.5 | 8.5 |
| –2.01 to –3.0 | 5.6 | 0.0 | 7.0 | 0.0 | 2.8 | 2.8 |

CVLT-II: Semantic Clustering – Long Delay Free Recall (14.1%), Semantic Clustering – Short Delay Free Recall (23.9%), Long Delay Free Recall (32.4%), and Short Delay Free Recall (35.2).

*Regression analyses*

*Executive functions*. Results for the series of hierarchical multiple regression analyses examining the relationship between HbA1c, IL-6, CRP, and executive

functions are shown in Table 5. Overall, the predictors accounted for a significant proportion of the variance in the Stroop Color-Word test, Trail Making Test Part B, and Semantic Fluency. For both the Written and Oral versions of the Symbol Digit Modalities Test, the regression equation approached significance for HbA1c only. The regression equation for Phonemic Fluency did not reach significance.

For Stroop Color-Word, the full model accounted for a statistically significant proportion of the variation in the dependent measure, $R^2$ = 30.2%, $F(5,55) = 4.76$, $p < .01$. HbA1c accounted for no additional variance in the dependent measure above the covariates, $\Delta F(1,57) = .014$, $p < .91$. The addition of the two inflammatory markers to the model accounted for an additional 8.0% of the variance, $\Delta F(2,55) = 3.17$, $p < .05$. Among the inflammatory markers, only CRP made a significant unique contribution to the final model, $t(1,55) = 2.46$, $p < .02$, $sr^2$ = 7.7%, indicating that higher levels of CRP were associated with higher numbers of correct responses on Stroop Color-Word.

For Trail Making Test Part B, the full model accounted for a statistically significant portion of the variation in the dependent measure, $R^2$ = 41.0%, $F(5,56) = 7.79$, $p < .01$. The addition of HbA1c to the equation accounted for an additional 6.3% of the variance above the covariates, $\Delta F(1,58) = 5.88$, $p < .02$, indicating that higher levels of HbA1c were associated with longer times to complete the Trails B task. IL-6 and CRP accounted for an additional 2.9% of the variance in the dependent variable, although the change was not significant, $\Delta F(2,56) = 1.37$, $p = .26$.

For Semantic Fluency, the full model accounted for a statistically significant portion of the variance in the dependent measure, $R^2$ = 33.8%, $F(5,56) = 5.72$, $p < .01$. HbA1c accounted for no additional variance in the dependent measure above the

Table 5
*Hierarchical regression analyses of glycated hemoglobin, inflammatory markers, and cognitive measures tapping executive functions.*

| Criterion Variables | Step | Predictor Variables | Full Model ∃ | $R^2$ | $\Delta R^2$ |
|---|---|---|---|---|---|
| Stroop Color-Word | 1 | Age | -.45** | | |
| | | NAART | .06 | .22** | |
| | 2 | HbA1c | -.01 | | .00 |
| | 3 | IL6 | -.02 | | |
| | | CRP | .29* | | .08* |
| Trail Making Test Part B | 1 | Age | .44** | | |
| | | NAART | -.38 | .32** | |
| | 2 | HbA1c | .26* | | .06* |
| | 3 | IL6 | .07 | | |
| | | CRP | -.18 | | .03 |
| Semantic Fluency | 1 | Age | -.46** | | |
| | | NAART | .20† | .22** | |
| | 2 | HbA1c | .02 | | .00 |
| | 3 | IL6 | .27* | | |
| | | CRP | .16 | | .12* |
| Phonemic Fluency | 1 | Age | -.25* | | |
| | | NAART | .51** | .37** | |
| | 2 | HbA1c | .11 | | .01 |
| | 3 | IL6 | -.05 | | |
| | | CRP | .21† | | .04 |
| Symbol Digit Modalities - Written | 1 | Age | -.41** | | |
| | | NAART | .29* | .23** | |
| | 2 | HbA1c | -.21† | | .04† |
| | 3 | IL6 | -.02 | | |
| | | CRP | .21† | | .04 |
| Symbol Digit Modalities - Oral | 1 | Age | -.40** | | |
| | | NAART | .29* | .24** | |
| | 2 | HbA1c | -.21† | | .04† |
| | 3 | IL6 | -.07 | | |
| | | CRP | .20 | | .04 |

†$p < .10$; *$p < .05$; **$p < .01$

covariates, $\Delta F(1,58) = .007$, $p < .94$. The addition of the two inflammatory markers to the model accounted for an additional 8.0% of the variance, $\Delta F\ (2,56) = 4.86$, $p < .05$. Among the inflammatory markers, only IL-6 made a significant unique contribution to the final model, $t(1,56) = 2.30$, $p < .03$, $sr^2 = 6.3\%$, indicating that higher levels of IL-6 were associated with greater numbers of correct semantic fluency responses.

For the Symbol Digit Modalities Test - Written version, the full model accounted for a statistically significant portion of the variance in the dependent measure, $R^2 = 31.6\%$, $F(5,56) = 5.18$, $p < .001$. The addition of HbA1c to the model accounted for an additional 4.0% of the variance above the covariates, a change that approached significance, $\Delta F(1,58) = 3.23$, $p = .08$. An additional 4.1% of the variance in the dependent variable was accounted for by adding IL-6 and CRP to the model, although the change was not significant, $\Delta F(2,56) = 1.69$, $p = .19$. Among the individual predictors, contributions to the final model that approached significance were made by HbA1c (as described above) and CRP, $t(1,56) = 1.81$, $p = .08$, $sr^2 = 4.0\%$.

For the Symbol Digit Modalities Test – Oral version, the full model accounted for a statistically significant portion of the variance in the dependent measure, $R^2 = 31.3\%$, $F(5,56) = 5.11$, $p < .001$. The addition of HbA1c to the model accounted for an additional 4.2% of the variance in the dependent variable above the covariates, a change that approached significance, $\Delta F(1,58) = 3.34$, $p = .07$. Adding IL-6 and CRP to the model accounted for an additional 3.5% of the variance, although this change was not significant, $\Delta F(2,56) = 1.42$, $p = .25$.

For Phonemic Fluency, the full model accounted for a statistically significant portion of the variance in the dependent measure, $R^2 = 42.4\%$, $F(5,56) = 8.26$, $p < .001$.

The addition of HbA1c to the equation accounted for an additional 1.0% of the variance above the covariates, a change that was not statistically significant, $\Delta F(1,58) = .93$, $p = .34$. Adding IL-6 and CRP to the model accounted for an additional 4.1% of the variance, although this change was not statistically significant, $\Delta F(2,56) = 1.98$, $p = .15$. Among the inflammatory markers, only CRP made a contribution to the final model that approached significance, $t(1,56) = 1.98$, $p = .052$, $sr^2 = 4.0\%$.

*Verbal memory.* Results for the series of hierarchical multiple regression analyses examining the relationship between HbA1c, IL-6, CRP, and verbal memory are shown in Table 6. Overall, the regression equations accounted for significant amounts of the variance in CVLT-II Semantic Clustering – Short Delay Free Recall, CVLT-2 Long Delay Free Recall, and Logical Memory – Delayed Recall. For CVLT-II Short Delay Free Recall and Logical Memory – Immediate Recall, the variance accounted for by the regression equation approached significance. The regression equation for CVLT-II Semantic Clustering – Long Delay Free Recall did not reach significance.

For CVLT-II Semantic Clustering – Short Delay Free Recall, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2 = 20.2\%$, $F(5,56) = 2.84$, $p < .02$. The addition of HbA1c to the model accounted for an additional 6.5% of the variance in the dependent variable above the covariates, $\Delta F(1,58) = 4.71$, $p < .03$, indicating that higher levels of HbA1c were associated with reduced use of the semantic clustering strategy. IL-6 and CRP accounted for no additional variance in the dependent measure, $R^2 = .20\%$, $\Delta F(1,58) = 4.71$, $p < .03$.

Table 6
*Hierarchical regression analyses of glycated hemoglobin, inflammatory markers, and verbal memory measures.*

| Criterion Variables | Step | Predictor Variables | Full Model ∃ | $R^2$ | $\Delta R^2$ |
|---|---|---|---|---|---|
| CVLT-II Short Delay Free Recall | 1 | Age | -.14 | | |
| | | NAART | .12 | .02 | |
| | 2 | HbA1c | -.31* | | .09* |
| | 3 | IL6 | -.22† | | |
| | | CRP | .20 | | .06 |
| CVLT-II Short Delay Free Recall Semantic Clustering | 1 | Age | -.02 | | |
| | | NAART | .37** | .14* | |
| | 2 | HbA1c | -.27* | | .07* |
| | 3 | IL6 | -.04 | | |
| | | CRP | .03 | | .00 |
| CVLT-II Long Delay Free Recall | 1 | Age | -.25† | | |
| | | NAART | .15 | .10* | |
| | 2 | HbA1c | -.17 | | .03 |
| | 3 | IL6 | -.21 | | |
| | | CRP | .19 | | .06 |
| CVLT-II Long Delay Free Recall Semantic Clustering | 1 | Age | .02 | | |
| | | NAART | .20 | .04 | |
| | 2 | HbA1c | -.23† | | .05† |
| | 3 | IL6 | -.17 | | |
| | | CRP | .10 | | .03 |
| Logical Memory Immediate Recall | 1 | Age | -.18 | | |
| | | NAART | .33* | .14** | |
| | 2 | HbA1c | -.15 | | .02 |
| | 3 | IL6 | -.09 | | |
| | | CRP | .07 | | .01 |
| Logical Memory Delayed Recall | 1 | Age | -.11 | | |
| | | NAART | .30* | .10* | |
| | 2 | HbA1c | -.21 | | .04 |
| | 3 | IL6 | -.17 | | |
| | | CRP | .17 | | .04 |

†$p < .10$; *$p < .05$; **$p < .01$

For CVLT-2 Long Delay Free Recall, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 17.8%, $F(5,56)$ = 2.43, $p < .05$. Adding HbA1c to the model did not account for a statistically significant amount of the variance in the dependent variable above the covariates, $\Delta R^2$ = 2.5%, $\Delta F$ (1,58) = 1.62, $p$ = .21. The addition of IL-6 and CRP to the model also did not account for a significant amount of the variance in the dependent variable, $\Delta R^2$ = 5.7%, $\Delta F(2,56)$ = 1.95, $p$ = .15.

For Logical Memory – Delayed Recall, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 18.2%, $F(5,56)$ = 2.48, $p < .04$. Adding HbA1c to the model did not account for a statistically significant amount of the variance in the dependent variable above the covariates, $\Delta R^2$ = 3.9%, $\Delta F(1,58)$ = 2.62, $p$ = .11. The addition of IL-6 and CRP to the model also did not account for a significant amount of the variance in the dependent variable, $\Delta R^2$ = 4.1%, $\Delta F$ (2,56) = 1.41, $p$ = .25.

For CVLT-II Short Delay Free Recall, the full model accounted for a portion of the variance in the dependent measure that approached significance, $R^2$ = 17.3%, $F(5,56)$ = 2.34, $p$ = .053. Adding HbA1c to the model accounted for a statistically significant amount of the variance in the dependent variable above the covariates, $\Delta R^2$ = 8.8%, $\Delta F$ (1,58) = 5.76, $p < .02$, indicating that higher levels of HbA1c was associated with fewer words recalled. The addition of IL-6 and CRP to the model did not account for a significant amount of the variance in the dependent variable, $\Delta R^2$ = 6.3%, $\Delta F(2,56)$ = 2.12, $p$ = .13. Among the inflammatory markers, only IL-6 made a contribution to the final model that approached significance, $t(1,56)$ = -1.71, $p$ = .09, $sr^2$ = 4.3%.

For Logical Memory – Immediate Recall, the full model accounted for a portion of the variance in the dependent measure that approached significance, $R^2$ = 17.5%, $F(5,56) = 2.37$, $p = .051$. Adding HbA1c to the model did not account for a statistically significant amount of the variance in the dependent variable above the covariates, $\Delta R^2$ = 2.1%, $\Delta F(1,58) = 1.48$, $p = .23$. The addition of IL-6 and CRP to the model also did not account for a significant amount of the variance in the dependent variable, $\Delta R^2$ = 1.0%, $\Delta F(2,56) = .33$, $p = .72$.

For CVLT-II Semantic Clustering – Long Delay Free Recall, the full model did not account for a statistically significant amount of the variance in the dependent variable, $R^2$ = 11.5%, $F(5,56) = 1.45$, $p = .22$. The addition of HbA1c to the model accounted for a portion of the variance in the dependent variable above the covariates that approached significance, $\Delta R^2$ = 4.9%, $\Delta F$ (1,58) = 1.48, $p = .08$. Adding IL-6 and CRP to the equation did not add significantly to the variance accounted for in the dependent variable, $\Delta R^2$ = 2.9%, $\Delta F(2,56) = .92$, $p = .41$.

*Attention, language, visuospatial judgment, and fine motor dexterity*. Results for the series of hierarchical multiple regression analyses examining the relationship between HbA1c, IL-6, CRP, and the array of neuropsychological measures measuring attention, language, visuospatial judgment, and fine motor dexterity are shown in Table 7. Overall, the regression equations accounted for significant amounts of the variance in Digits Forward, Digits Backward, Boston Naming, and Grooved Pegboard for both Dominant and Non-dominant hands. The regression equation for Judgment of Line Orientation did not reach significance.

Table 7
*Hierarchical regression analyses of glycated hemoglobin, inflammatory markers, and cognitive function measures.*

| Criterion Variables | Step | Predictor Variables | Full Model ∃ | $R^2$ | $\Delta R^2$ |
|---|---|---|---|---|---|
| Digits Forward | 1 | Age | -.30* | | |
| | | NAART | .30 | .19** | |
| | 2 | HbA1c | -.06 | | .00 |
| | 3 | IL6 | .07 | | |
| | | CRP | .03 | | .01 |
| Digits Backward | 1 | Age | -.21† | | |
| | | NAART | .49** | .32** | |
| | 2 | HbA1c | -.01 | | .00 |
| | 3 | IL6 | -.04 | | |
| | | CRP | .06 | | .00 |
| Boston Naming | 1 | Age | -.19 | | |
| | | NAART | .46** | .25** | |
| | 2 | HbA1c | -.11 | | .01 |
| | 3 | IL6 | -.07 | | |
| | | CRP | .19 | | .03 |
| Judgment of Line Orientation | 1 | Age | -.18 | | |
| | | NAART | .20 | .08† | |
| | 2 | HbA1c | -.16 | | .02 |
| | 3 | IL6 | -.16 | | |
| | | CRP | .07 | | .02 |
| Grooved Pegboard - Dominant | 1 | Age | .32* | | |
| | | NAART | -.04 | .13** | |
| | 2 | HbA1c | .15 | | .02 |
| | 3 | IL6 | .31* | | |
| | | CRP | -.23† | | .11* |
| Grooved Pegboard – Non-dominant | 1 | Age | -.11 | | |
| | | NAART | .30* | .16** | |
| | 2 | HbA1c | -.21 | | .06* |
| | 3 | IL6 | -.17 | | |
| | | CRP | .17 | | .08* |

†$p < .10$; *$p < .05$; **$p < .01$

For Digits Forward, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 20.1%, $F(5,56) = 2.82$, $p < .02$. No additional variance above the covariates was accounted for by the addition of HBA1c, $\Delta R^2$ = .30%, $\Delta F(1,58) = .20$, $p = .65$, or the inflammatory markers IL-6 and CRP, $\Delta R^2$ = .50%, $\Delta F(2,56) = .17$, $p = .84$.

For Digits Backward, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 32.3%, $F(5,56) = 5.35$, $p < .001$. No additional variance above the covariates was accounted for by the addition of HBA1c, $\Delta F(1,58) = .003$, $p = .96$, or the inflammatory markers IL-6 and CRP, $\Delta R^2$ = .40%, $\Delta F(2,56) = .15$, $p = .86$.

For Boston Naming, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 29.8%, $F(5,56) = 4.74$, $p < .001$. No additional statistically significant variance above the covariates was accounted for by the addition of HBA1c, $\Delta R^2$ = 1.2%, $\Delta F(1,58) = .91$, $p = .34$, or the inflammatory markers IL-6 and CRP, $\Delta R^2$ = 3.2%, $\Delta F(2,56) = 1.29$, $p = .28$.

For Grooved Pegboard – Dominant Hand, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2$ = 25.5%, $F(5,56) = 3.83$, $p < .005$. The additional variance above the covariates accounted for by the addition of HbA1c was not statistically significant, $\Delta R^2$ = 2.0%, $\Delta F$ (1,58) = 1.35, $p$ = .25. Adding IL-6 and CRP to the equation accounted for a statistically significant amount of variance in the dependent variable above that contributed by the covariates, $\Delta R^2$ = 10.7%, $\Delta F(2,56) = 4.02$, $p < .02$. Among the inflammatory markers, IL-6 made a unique and statistically significant contribution to the variance in the final model, $t$(1,56)

= 2.54, $p < .01$, $sr^2 = 8.6\%$, indicating that higher levels of IL-6 were associated with longer time to completion on Grooved Pegboard – Dominant. The unique contribution of CRP to the final model approached significance, $t(1,56) = -1.91$, $p = .062$, $sr^2 = 4.8\%$.

For Grooved Pegboard – Non-dominant Hand, the full model accounted for a statistically significant amount of the variance in the dependent measure, $R^2 = 29.9\%$, $F(5,56) = 4.78$, $p < .001$. HbA1c accounted for 5.9% of additional variance in the dependent measure above the covariates, $\Delta F(1,58) = 4.39$, $p < .04$. Adding IL-6 and CRP to the model accounted for an additional 8.2% of the variance in the dependent variable, $\Delta F(2,56) = 3.27$, $p < .045$. Among the inflammatory markers, only IL-6 made a unique and statistically significant contribution to the variance in the model, $t(1,56) = 2.39$, $p < .02$, $sr^2 = 3.0\%$, indicating that higher levels of IL-6 were associated with longer time to completion on Grooved Pegboard – Non-dominant.

For Judgment of Line Orientation, the full model did not account for a statistically significant amount of the variance in the dependent variable, $R^2 = 12.9\%$, $F(5,56) = 1.66$, $p = .16$. No additional statistically significant variance above the covariates was accounted for by the addition of HBA1c, $\Delta R^2 = 2.3\%$, $\Delta F(1,58) = 1.48$, $p = .23$, or the inflammatory markers IL-6 and CRP, $\Delta R^2 = 2.3\%$, $\Delta F(2,56) = .724$, $p = .49$.

*Further exploratory analyses*

The following analyses were conducted in order to determine whether any additional information could be obtained that could aid in the interpretation the results that have been presented. These analyses must be considered exploratory, however, because removing cases or adding variables to these analyses results in a reduction in the power to detect effects. The previous analyses employed six variables and thus had

already reached the power limits for this design and sample size (Field, 2005). Nonetheless, the following analyses were conducted in order to determine whether any effects were present that were large enough to be detected under these limited circumstances.

*Investigation of CRP effects.* In the original analyses, the results indicated that higher levels of CRP were associated with improved cognitive performance. In order to further examine the direction of the relationship between CRP and cognitive performance, the cases with the highest levels of CRP (> 10mg/L; $n$ = 22) were removed and the original analyses were performed again. This modification of the sample yielded a change in the direction of the relationship between CRP and cognition for all relevant criterion variables, such that higher levels of CRP were associated with worse performance on Stroop Color-Word, Semantic Fluency, Phonemic Fluency, and Symbol Digit Modalities – Written version. This result is suggestive of a U-shaped function in which very high levels of CRP (< 10 mg/L) are associated with improved performance on the cognitive measures tapping executive functions, whereas for those patients with levels of CRP falling in the low to high risk range, higher levels of CRP are associated with poorer executive function performance.

*Relationship with other covariates: Depression and duration of diabetes.* In order to determine whether depression accounted for any of the variance in the criterion variables, all of the original regression analyses were re-run with GDS score entered as a covariate at the second step. GDS score did not contribute significantly to the variance in the model either at the second step or in the final model for any of the measures of executive function or verbal memory, nor did it change any of the patterns

of effects already reported. Among the remaining neuropsychological criterion variables, the addition of GDS was significant only for Digits Backward. Specifically, the full model accounted for 41.1% of the variance in the dependent variable, $F(6,55) = 6.39$, $p < .001$, as compared with 32.3% for the same model without GDS included. Adding GDS to the model accounted for an additional 8.2% of variance above that contributed by the covariates, $\Delta F(1,58) = 7.98$, $p < .006$. GDS made a unique and statistically significant contribution to the variance in the full model, $t(1,55) = 2.86$, $p < .005$, $sr^2 = 3.0\%$, indicating that higher scores on the GDS were associated with improved Digits Backward performance.

In order to determine whether duration of diabetes accounted for any of the variance in the criterion variables, all of the original regression analyses were re-run with duration of diabetes entered as a covariate at the second step. The rationale for entering duration of diabetes before HbA1c is that duration might be associated with long-term neurological changes (Awad et al., 2004), whereas HbA1c may have a relatively transient effect on cognition in comparison. Duration of diabetes did not contribute significantly to the variance in the dependent variable for any of the measures of executive function. Among measures of verbal memory, duration of diabetes made significant contributions to the models for CVLT-II Short Delay Free Recall and Logical Memory Immediate Recall. Duration of diabetes also contributed significantly to the variance in the model for the Boston Naming Test.

For CVLT-II Short Delay Free Recall, the full model accounted for 21.9% of the variance in the dependent variable, $F(6,55) = 2.58$, $p < .03$, an increase of 4.6% over the same model without duration of diagnosis, and a shift to statistical significance. The

addition of duration of diabetes to the model accounted for an additional 9.5% of the variance in the dependent variable above the covariates, $\Delta F(1,58) = 4.26$, $p < .01$. Whereas HbA1c was statistically significant and IL-6 approached significance in the previous model, those effects were eliminated with the addition of duration of diabetes.

For Logical Memory Immediate Recall, the full model accounted for 24.0% of the variance in the dependent variable $F(6,55) = 2.90$, $p < .02$, an increase of 6.5% over the same model without duration of diabetes. The addition of duration of diabetes to the model accounted for an additional 8.1% of the variance in the dependent variable above the covariates, $\Delta F(1,58) = 6.05$, $p < .02$. As in the model without duration of diabetes, however, no additional variance above the covariates was contributed by adding HbA1c, IL-6 and CRP to the model.

For the Boston Naming Test, with duration of diabetes included, the full model accounted for 33.9% of the variance in the dependent variable, $F(6,55) = 4.70$, $p < .001$. The addition of duration of diabetes to the model accounted for an additional 5.3% of the variance in the dependent variable above the covariates, $\Delta F(1,58) = 8.57$, $p < .001$. As in the previous model without duration of diabetes, the addition of HbA1c, IL-6 and CRP to the model did not account for a statistically significant amount of variance in the dependent variable above the covariates. In the final model, the contribution to the model made by duration of diagnosis only approached significance, $t(1,55) = -1.86$, $p = .07$, $sr^2 = 4.1\%$.

# CHAPTER 4: DISCUSSION

The elderly African Americans with type 2 diabetes who served as participants in this study generally performed in the average range on neuropsychological measures. There were some exceptions, though. Participants were mildly impaired on both the written and oral versions of the Symbol Digit Modalities test, demonstrated low average performance on three of the CVLT-II scores (Short and Long Delay Free Recall, and Long Delay Semantic Clustering), and low average performance on Grooved Pegboard for both hands. Thus, these results provide partial support for the hypothesis that these participants would be impaired in some aspects of executive function and on measures of verbal memory that require intact executive functions for adequate performance. Mean scores for all other executive function measures were in the average range, however, which is inconsistent with that hypothesis. The low average performances on the CVLT-II are consistent with the hypothesis, but this low average range was not significantly different from average.

The findings of the present study are consistent with the hypothesis that chronic hyperglycemia would be inversely related to performance on measures of executive function and verbal memory that tap executive functions, but not to other neuropsychological measures. Higher HbA1c scores were significantly associated with poorer performance on Trail Making Test Part B, CVLT-II Short Delay Free Recall, and CVLT-II Semantic Clustering – Short Delay Free Recall, and approached significance in predicting poorer performance on Symbol Digit Modalities Test – Written and Oral versions, and CVLT-II Semantic Clustering – Long Delay Free Recall.

The observed association between higher HbA1c and impaired performance on a word list learning task is consistent with previous findings (Gradman et al., 1993; Jagusch, Cramon, Renner, & Hepp, 1992; Perlmuter et al., 1984; Reaven et al., 1990), and extends the previous findings by demonstrating a similar effect in an elderly African American sample. A few studies have reported no significant relationship between HbA1c and word list learning. For example, Lowe and colleagues (Lowe et al., 1994) employed another widely used word list learning test, the Rey Auditory Verbal Learning Test (RAVLT), and found no group differences between diabetics and controls. Their sample consisted of Native Americans, however, and was younger, ranging in age from 45 to 75 years old. Zaslavsky and colleagues (Zaslavsky, Gross, Chaves, & Machado, 1995) employed a word list learning task that, similar to the CVLT-II, involved the five auditory presentations of a word list. Unlike the CVLT-II, however, the task used by Zaslavsky and colleagues entailed free recall trials occurring only after the first and fifth list presentations, and then again after a 15-minute interval. In contrast, the CVLT-II consists of free recall trials occurring following each of the five list presentations, and then again after a brief delay and a longer, 20-minute interval. Thus, the encoding process for the word list-learning task used by Zaslavsky and colleagues may be qualitatively different that that engaged in during CVLT-II. Specifically, the CVLT-II offers many more opportunities to reinforce the learning of the list words than does the other task. No other information was provided about the types of words in the lists used by Zaslavsky and colleagues or their semantic relationships, which also may have accounted for some of the difference in the outcomes.

In the present study chronic hyperglycemia and inflammation were not significantly associated with immediate or delayed recall performance on a paragraph recall task. This result is inconsistent with those of a previous study in which experimentally-induced acute hyperglycemia was associated with a relative decline in recall on an auditory-verbal paragraph recall task (Greenwood et al., 2003). There may be differences in the relative influence on cognitive function of acute versus chronic hyperglycemia, however. It may be that those individuals in the present study with higher acute glucose levels performed more poorly on this task, but this could not be determined because acute glucose levels were not measured. The present results do support a relationship between duration of diagnosis (i.e., the effects of long-term chronic hyperglycemia) and verbal learning and memory decrements, however. Specifically, longer duration of diabetes diagnosis was associated with poorer immediate recall performance both on a paragraph recall task and on a verbal word list-learning task. This result is similar to those in a previous study (Elias et al., 1997) in which impaired immediate and delayed word list-learning were related to duration of diabetes diagnosis. Further, in the present study there was a trend toward an association between longer duration of diagnosis and poorer performance on a confrontation picture-naming task that relies heavily upon intact semantic retrieval abilities. These deficits are similar to the classic pattern of cognitive impairment observed in dementia of the Alzheimer's type, which involves rapid forgetting and impaired semantic retrieval (Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006). It is unclear whether diabetes increases the risk of Alzheimer's disease (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004) or not (Akomolafe et al., 2006),

but the present results suggest that those with a longer duration of diagnosis are more likely to manifest a pattern of cognitive performance that is similar to that found among individuals with dementia of the Alzheimer's type.

The present finding of the association between higher HbA1c and impaired Trails B performance is consistent with the results of one previous study (Reaven, 1991) in which HbA1c was inversely related to Trails B performance in both a group of 29 elderly type 2 diabetes patients, and in the group of 30 demographically similar, healthy controls. This finding is inconsistent with the results of several other studies, however. For example, in one study, 50 Caucasian and African American adults with type 2 diabetes and 50 demographically similar, healthy controls failed to differ on Trails B after controlling for age, sex, race, and estimated IQ (Ryan & Geckle, 2000a). Notably, however, the participants were mostly middle-aged, ranging in age from 34 to 65 ($M$ = 50.8). In another study, elderly type 2 diabetics and controls did not differ on Trails B (Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995). The group sizes were relatively small, however, ($n$s = 20 and 22, respectively), and they used means comparisons instead of regressions, and thus, could not control for the effects of age and education. In sum, it may be that Trails B performance varies with HbA1c levels in elderly adults, but sufficiently large sample sizes and appropriate statistical methods are required in order to observe this effect.

This is the first study to examine the effects of inflammation and chronic hyperglycemia in a group comprised solely of adults with type 2 diabetes. Zero-order correlations between glycated hemoglobin and inflammation indicated that HbA1c was not related to either IL-6 ($r$ = -.08; $p$ = .53) or CRP ($r$ = .00; $p$ = .99). This result may

have been an artifact of the study methods, however, given that in most cases HbA1c and the inflammatory markers were measured on different days. Thus, it is possible (although unclear from the literature) that HbA1c is typically more highly related with the inflammatory markers. Notably, the inflammatory markers were also not highly correlated with each other ($r$ = .26, $p$ < .04). The fact that these predictors had so little statistical relationship to each other suggested that different patterns of effects for HbA1c and each of the inflammatory markers might be expected. Indeed, there was very little overlap in the effects of the three predictor variables. Higher IL-6 significantly predicted slower completion times on Grooved Pegboard – Dominant hand, but also was associated with a greater number of correct responses on Semantic Fluency; IL-6 approached significance in predicting poorer performance on CVLT-II Short Delay Free Recall. CRP was unique among the predictor variables in this study in that, contrary to the study hypothesis, higher CRP levels were associated with improved cognitive performance. Specifically, higher CRP was significantly associated with better performance on Stroop Color-Word, and approached significance in predicting better performance on Phonemic Fluency, Symbol Digit Modalities – Written version, and Grooved Pegboard – Dominant hand. This finding is inconsistent with the majority of the literature, which tends to show an inverse relationship between CRP and cognition (Engelhart et al., 2004; Schmidt et al., 2002; Teunissen et al., 2003; Yaffe et al., 2004; Yaffe et al., 2003). One study, however, showed that in older adults with the APOE4 allele, higher CRP was associated with lower rates of dementia and cognitive impairment without dementia, whereas in a control group without the APOE4 allele, higher CRP was associated with increased rates of dementia and cognitive impairment

without dementia (Haan, Aiello, West, & Jagust, 2007). Further, in those without the APOE4 allele, CRP was significantly lower. They interpreted the results as suggesting that in those with APOE4, high CRP may be a marker of better immune function, leading to reduced rates of dementia and Alzheimer's disease. In the present study, an exploratory analysis was conducted in which the cases with the highest levels of CRP were removed from the analyses. Results showed that with the CRP levels in the analysis reduced to the range of low to high risk only, the direction of the relationship reversed between CRP and several of the criterion variables--particularly executive measures--such that CRP was inversely related to cognitive performance. This result suggests that it was primarily those with very high CRP (> 10 mg/L) driving the effect of higher CRP being related to improved performance on cognitive measures. APOE4 was not assessed in these participants ($n$ = 22), but it seems unlikely that all of the participants with the highest levels of CRP in this study had the APOE4 allele. It may be, however, that higher CRP is associated with better cognitive functioning (possibly via improved immune functioning) in some groups, including those with the APOE4 allele, and may be related to other as yet unknown factors, as well.

While the majority of studies of diabetes and cognition have used predominantly or solely Caucasian samples, and a few had mixed-race samples (Ryan & Geckle, 2000a), this is the first study to examine the relationship between HbA1c and cognition in a group of older adult African Americans with type 2 diabetes. One study examining the relationships of HbA1c, blood pressure, and several other indicators of cardiovascular risk in middle aged and older adult (43-82 years) African Americans found that HbA1c was significantly related to better performance on Digits Forward, and

marginally associated with better performance on an executive function screening measure (Izquierdo-Porrera & Waldstein, 2002). This study differs from the present study in several important ways, however, including the inclusion of middle aged participants, a small sample size (*n* = 43), and the fact that only 19% of their sample was diabetic. Another study employing a small sample (*n* = 43) of African American adults found that a summary cardiovascular risk score was associated with increased risk of impaired performance on a set of executive function tasks, but not on visuospatial or memory tests (Pugh et al., 2003). The executive function tasks included Trails B, Phonemic and Semantic Fluency, and Letter-Number Sequencing, while the memory tests included Logical Memory Immediate and Delayed Recall, and a visual memory task. Although only 12% (*n* = 5) of the sample had a self-reported diabetes diagnosis, and the sample size was small, the findings of this study are consistent with the present results, and provide additional evidence for the finding that in elderly African Americans, cardiovascular risk factors are associated with impairments in executive functions, but not contextual verbal memory.

Consistent with the study predictions, levels of HbA1c, IL-6, and CRP were not significantly associated with performance on measures of visuospatial judgment, language, simple auditory attention, or fine motor dexterity. Contrary to that prediction, however, significant effects of the predictor variables were observed for Grooved Pegboard, both for the Dominant and for the Non-dominant hand. The Grooved Pegboard task has rarely been used in studies of older adults with type 2 diabetes, but there is a small amount of evidence indicating that this population may have difficulty with this task. For example, psychomotor slowing among middle aged diabetics has

been reported, results that were based in part on impaired Grooved Pegboard performance (Ryan & Geckle, 2000a). It was also demonstrated that improving glucose regulation in a small group of elderly diabetics (*n* = 16*)* yielded improved performance on a number of neuropsychological measures, including the Grooved Pegboard test (Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993). The results of the present study add to this small group of evidence suggestive of psychomotor slowing and/or reduced fine motor dexterity in older adults with type 2 diabetes.

Digits Backward performance was not significantly impaired in this sample of individuals with diabetes, nor was it significantly predicted by chronic hyperglycemia or inflammation. Although Digits Backward, as a working memory test, is often grouped with measures of executive function, it was not predicted to be impaired in this study because it was not impaired in previous studies of cognitive function in older adults with diabetes (Atiea, Moses, & Sinclair, 1995; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; Reaven et al., 1990; U'Ren et al., 1990) or who were deemed to be at high risk for diabetes (Vanhanen et al., 1997). The failure to observe a significant effect of diabetes on this working memory task may be attributable both to the difficulty of the task for older adults, and a restriction in the range of scores for older adults. In other words, this task may be very difficult for all adults in that age range. Thus, whether the comparison is made with healthy controls or with published normative data, the performance of older adults with diabetes appears to fall within the average range. Further, if most older adults correctly recall very few digit strings on Digits Backward, the range of scores would be restricted, reducing the correlation with other variables. A large sample size can increase the

chances of detecting a small effect. The previous studies with null findings for Digits Backward had diabetic sample sizes ranging from 29 to 43 participants. The fact that no significant effects were detected for Digits Backward even with the larger sample in the present study provides more evidence for the lack of association between hyperglycemia and performance on this task. The present results also extend those results to suggest a lack of association between Digit Span performance and inflammation, as represented by levels of IL-6 and CRP. Notably, Digits Backward performance was predicted by one variable in this study. Specifically, those with higher scores on the depression screening measure (GDS) performed significantly better on Digits Backward than those with lower GDS scores. Given that depression is a well-known predictor of impaired cognitive functioning, particularly on measures such as Digits Backward that require intact attentional and working memory abilities, this result was unexpected. It should be noted however, that the majority of participants' GDS scores fell in the non-depressed range, and those with the highest scores fell in the mildly depressed range ($n$ = 5). Given that there were no moderately or severely depressed individuals included in the sample, it may be that the mildly elevated GDS scores and the higher Digits Backward scores were both reflective of effort. Specifically, it is possible that those participants who were willing to admit to more symptoms associated with depression may also have been more cooperative with the testing process overall, and may have devoted more effort to testing, earning higher scores on the challenging Digits Backward task.

There are several weaknesses in the present study that limit the generalizability of the results. First, the sample size was relatively small. Unfortunately, relatively small

sample sizes characterize much of the literature examining the relationships between diabetes and cognition. A larger sample would have allowed for the detection of any smaller effects that may have been present. Further, the relatively low number of participants limited the number of variables that could be assessed in each analysis. Thus, while some of the covariates that were measured may have accounted for a statistically significant amount of additional variance in a larger sample, given the small sample size there was not enough power to detect any additional effects related to these additional variables. Having more participants would allow for the testing of more complex models of the potential relationships between variables. While there were a number of variables that were measured but not included in the study because of the small sample size, there were still other variables that were not measured that may have been informative. For instance, it would likely have been useful to have measures of acute glucose levels, blood lipid levels, and current medications.

Another weakness of this study is the lack of a control group. Having a control group would have allowed for the direct comparison of scores on cognitive measures with a healthy, age- and education-matched control group rather than relying upon published normative data to interpret test results. In addition, having a control group would have allowed for the examination of whether or not the observed pattern of relationships among IL-6, CRP, and cognition would also hold for individuals without type 2 diabetes. Unfortunately, despite employing a number of methods in an attempt to recruit controls, only two control participants were tested. Diabetic participants were recruited via phone calls to individuals listed in the patient database in the diabetes

clinic. Perhaps obtaining access to a list of patients from a preventative medicine clinic would yield more fruitful recruiting results for controls.

Another weakness of the study was the small number of men in the sample. Reportedly, the research recruitment of African American males can be especially problematic (M. Norman, personal communication, May 25, 2007). Greater wariness about participating in research among African Americans has been documented in a study (Corbie-Smith, Thomas, & St. George, 2002) in which results indicated that distrust of research was significantly higher among males. Suggestions for increasing research recruitment success in the African American community included engaging in ongoing community involvement even when research recruitment is not occurring.

In summary, this research advances our understanding of the ways in which type 2 diabetes impairs cognition in older adults, and the potential mechanisms underlying such cognitive deficits. While most studies examining this topic have focused on older adult Caucasians, this study was the first specifically aimed at examining cognitive functioning in older African-Americans with type 2 diabetes. Further, this is the first study to examine the impact of both chronic hyperglycemia and inflammation on cognitive functioning in a group of older adults with type 2 diabetes. Results showed that, on average, cognitive functioning was in the average range in this sample of older African American adults with type 2 diabetes. A certain proportion of the group, however, displayed significant cognitive deficits and, as predicted, those deficits were predominantly in executive functioning rather than in the domain of memory. In future research it will be important to establish which variables best account for the predominantly executive cognitive deficits among certain older adults with type 2

diabetes. Based on the pattern of effects observed in the present study, it appears that chronic and acute glucose levels would be important predictors, and that using a larger sample size would allow for the detection of smaller effect sizes on the various executive functioning measures. This research is important because extensive evidence indicates that cognitive impairment limits the capacity to self-manage medical problems and follow medical recommendations in various medical populations. In order to adhere to a diabetes management plan, a patient must not only remember medical instructions, but must also have the cognitive capacity necessary to implement them correctly and consistently (Park & Kidder, 1996). Results of one study suggest that executive functioning and working memory are critical predictors of medication adherence. Specifically, a composite of executive function and working memory tasks was the only significant predictor of medication adherence in a group of 95 elderly adults when entered into a regression equation with several other predictors, including age, mental status exam score, a composite memory test score, education, illness severity, financial well-being, and depression (Insel, Morrow, Brewer, & Figueredo, 2006). Given that a portion of older adults with type 2 diabetes exhibit executive function deficits, future research should investigate whether the executive deficits observed in some older adults with type 2 diabetes are also predictive of poor medication adherence.

## CHAPTER 5: BIBLIOGRAPHY

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