Impact of Age and Metabolic Dysfunction on Memory and Executive Functions among Older Persons with Type 2 Diabetes Mellitus

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Abstract

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by

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The overall goal of the current study was to elucidate the impact of Type 2 diabetes mellitus (DM) on cognition among older persons (age 65 and over). Attention was paid to controlling for medical illnesses that are comorbid with DM and that have been shown to impair cognition in their own right (i.e., hypertension [HTN] and heart disease [HD]). We also sought to examine the extent to which increasing age impairs cognition among older persons with DM.

We investigated whether or not individuals with DM perform worse than individuals with HTN, HTN and HD, and healthy controls (HCs) on the free recall portion of the Free and Cued Selective Reminding test (FCSRT); subtests from the Consortium to Establish a Registry for Alzheimer's disease (CERAD): immediate and delayed recall word list (WL) and the Figure recall test; Verbal Fluency: category; and Clock Drawing tasks.

The results revealed that on the FCSRT and CERAD Figure recall, both the DM and HTN+HD groups recalled fewer items relative to the HC group, whereas the HTN group was comparable to the HC group. There were no differences among the groups on the CERAD-WL tests. There were no group differences on the verbal fluency or the clock drawing tasks.

A significant effect of Age was found on the FCSR, CERAD-WL tests, verbal fluency, and clock drawing, such that the oldest-old (80 + years) performed significantly worse than the young-old (65 – 79 years).

We also examined whether or not an inverse relationship existed between blood glucose (HbA1c) and cognition among those with DM. A potential interaction between Age and HbA1c was also evaluated. Results revealed an inverse relationship between HbA1c and recall on the CERAD-WL tests. An interaction between Age and HbA1c occurred for both CERAD-WL tests and Verbal Fluency. For participants with low HbA1c, performance decreased with increasing age; however, among participants with high HbA1c, performance improved with increasing age.

The finding that both the DM and HTN+HD groups were impaired on the FCSR and CERAD Figure recall test suggests that HD might be implicated in cognitive impairment associated with DM. The results also suggest that elevated HbA1c has a negative impact on cognition.

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Introduction

Background and Research Question

The overall aim of the current study was to elucidate the relationship between Type 2 diabetes mellitus (DM) and cognition among older persons (e.g., age 65 and over). The first objective was to examine whether or not increasing age had a deleterious effect on individuals with DM relative to healthy controls (HC) and individuals with both hypertension and heart disease (HTN+HD). The background for this investigation was based on converging lines of inquiry from medical and neuropsychological literature. First, there was evidence to suggest that the structural and physiological changes associated with normal brain-aging appeared to be accelerated in DM, particularly among older persons (Awad, Gagnon, & Messier, 2004). Second, there was a large body of research demonstrating that as individuals age, performance on tests of cognition became more compromised (Mesulam, 2000). Finally, medical literature purported that increasing age often rendered one vulnerable to complications associated with medical illnesses such as DM. Thus, it was argued that accelerated brain aging associated with DM increased vulnerability to medical complications, and age-related cognitive decline would result in a greater degree of cognitive impairment with increasing age.

In order to methodically research this question, our first line of action was to rule out factors that might have acted as possible confounds. More specifically, cardiovascular disease (e.g. hypertension [HTN] and heart disease [HD]) have been shown to be highly comorbid with DM. Taken separately, these illnesses

have been suggested, albeit equivocally, to negatively impact cognition in their own right (Verhaeghen, Borchelt, & Smith, 2003). Thus, an investigation concerning the contribution of DM to cognitive impairment warranted careful attention paid to controlling for confounding medical illnesses.

According to Awad et al. (2004), few studies in this area have properly controlled for medical confounds, thus making it difficult to isolate the effect of DM on cognition. In addition to controlling medical confounds, our aim was to remove psychiatric confounds (e.g., depression and schizophrenia) and demographic confounds (e.g., years of education and premorbid intellectual functioning) that have been shown to correlate with performance on measures of cognition (see Mathuranath et al., 2003).

The second objective was to examine the extent to which metabolic factors, such as glycemic (blood sugar) control, impact the cognitive abilities of older persons with DM. The rationale for this aim rested on findings showing that poor glycemic control results in a plethora of severe complications, such as cardiovascular problems and blindness, and has been hypothesized to have a deleterious effect on the brain (Incalzi, Corsonello, Pedone, Corica, & Carosella, 2002)

Glycemic control is measured by the amount of glucose in hemoglobin, a molecule found in red blood cells. HbA1c is used as an indicator of glycosylated hemoglobin; the more glucose in the blood, the greater the level of HbA1c. HbA1c is measured every 3 to 4 months in a diabetic patient as that is the lifespan of a red blood cell (R.J. Louard, personal communication, July 13, 2005).

Cognition and Aging

In order to understand compromised cognitive ability associated with chronic medical illness among older persons, it is imperative to first gain a clear understanding of the patterns of cognitive decline and preservation among normal healthy individuals.

It is well-established that cognitive ability, as demonstrated by performance on neuropsychological tests, changes throughout the lifespan. Indeed, the literature is replete with investigations describing the atypical cognitive deficits associated with the dementias among older persons (e.g., Wright, McSweeny, & Kieswetter, 2004). However, there are also a number of inquiries detailing the normative cognitive changes among healthy, older persons without dementia. Research suggests that a certain degree of cognitive decline is associated with normal aging and that the pattern of cognitive degeneration is not uniform. That is, several cognitive domains remain generally intact across the lifespan while notable decline is observed in others. Bieliauskus (2001) purports that the areas most susceptible to age-related change are speed of information processing, complex attention, reasoning and executive functioning, visuospatial processing, recall memory, and working memory.

Attention. With respect to attention, age appears to have a greater effect on the more complex aspects of attention relative to simpler attentional processes. Complex attention includes divided attention, selective attention, and vigilance. Simple attention (e.g., visual motor processing) shows little change over time (Filley & Cullum, 1994).

Executive Function. Tests of reasoning and executive functioning also show sensitivity to increasing age (Cavenaugh & Blanchard-Fields, 2002). In a study examining executive function throughout the lifespan, Zelazo, Craik, and Booth (2004) found that executive functions, such as the ability to sort, plan, and organize, reached a peak during early adulthood and then gradually declined around age 60.

Memory (immediate recall). Decline in memory is said to be a common complaint as individuals age. A gradual decline in memory functioning has been shown to occur after age 50, with a more rapid drop off in the 80's (Haaland, Price, & Larue, 2003). However, it appears that certain aspects of memory are more sensitive to the aging process than others. Research has shown that the capacity for immediate recall starts degrading as early as age 30. However, investigators have found little interaction between increasing age and the capacity for recognition (Festinau, Denberg, & Abeles, 2003). This differential decline has been explained as being secondary to reduced efficiency of working memory, which is a faculty of attention, as well as a decrement in the ability to screen out competing information (i.e., selective attention), both of which are essential for immediate recall but presumably less important for recognition (Hasher & Zacks, 1988; Wright et al., 2004).

Working Memory. Imaging studies tend to support the finding of a decrease in efficiency during working memory tasks. Research has shown that the neural substrates underlying working memory and attention (i.e., frontal lobes) are recruited more frequently in working memory tasks among older persons relative to younger (Reuter-Lorenz, Stanczack & Miller, 2000).

Functional imaging studies examining normal cognitive functioning during memory tasks indicate that the aged brain tends to activate more widespread networks, with more bilateral activation during recall of verbal material. Recruitment of additional networks is often interpreted as a reflection of an inefficient system (Cabeza, 1997). Moreover, the frontal lobes have been posited to be vulnerable to aging (Mesulam, 2000). Accordingly, investigators suggest an inverse relationship between increasing age and the ability to encode to-be-remembered information. Specifically, older adults have been purported to be less efficient with respect to organizing information into meaningful associations necessary to facilitate recall. This capacity is said to be mediated by the frontal lobes (see Cavenaugh & Blanchard-Fields, 2002).

Source Memory. Another aspect of memory that has been shown to be sensitive to increasing age is source memory. Source memory refers to the ability to remember where information was first learned. Older persons perform less well on tests of source memory and are more susceptible to false memories (Cavenaugh & Blanchard-Fields, 2002).

Semantic Memory. Semantic memory refers to the generic knowledge about the meaning of words (Tulving, 1983) and is typically retrieved automatically (Wiggs, Weisbberg, & Martin, 1999). There is considerable evidence showing decrements in semantic memory among individuals with Alzheimer's dementia (Salmon, Butters, & Chan, 1999) but there remains debate as to whether or not semantic memory declines with normal aging. However, emerging evidence shows that the capacity for semantic memory begins to decline at age 70 (Barresi et al., 2000). Nilsson (2003) demonstrated an

increase in semantic memory functioning up to age 60, after which there is a significant decrease in functioning.

Areas of Preservation. As previously mentioned, there are several aspects of cognitive functioning that have been suggested to be impervious to the aging process. Vocabulary and verbal comprehension appear to be well-preserved in optimally healthy older persons (see Wright et al., 2004). Additionally, older persons tend to do well on certain types of memory tests, including those that assess recognition, autobiographical, and implicit memory (Fleischman & Gabrielli, 1998). Finally, according to Baltes and Staudinger (2000), young and older persons perform equally well when solving problems that arise in daily living based on practical knowledge and experience.

Neurology of the Normal Aging Brain

There are a number of neurological changes associated with the healthy aging brain. Examinations utilizing in vivo imaging, such as computed tomography (CT), have revealed an increase in lateral ventricular size, indicating central atrophy, and an increase in sulci size, which is a marker of cortical atrophy (Raz, 1996). Volumetric MRI indicates that the correlation between age and cerebral volume is approximately -.40 (Trollor & Valenzuela, 2001). These findings are consistent with other volumetric studies. An examination involving 18-77 year-old participants reported a substantial, regionally selective volumetric decline of a magnitude of 5% per decade. Mueller et al. (1998) found that healthy, cognitively intact older persons, aged 85-93, had smaller brain volumes relative to 75-84 year old or 66-74 year old individuals and that all three groups within a 3-8 year follow-up period showed a loss of 0.01 – 0.06 cm^3 per year in

the medial temporal lobes. However, there was no difference in the rate of decline among the three age groups.

There is a line of thinking suggesting that frontal structures are particularly sensitive to the effects of both normal and pathological aging relative to other cortical association areas. Indeed, converging evidence lends support to this hypothesis. Studies have shown that prefrontal atrophy is about twice that found in the temporal or parietal neocortex (Murphy, DeCarli, & McIntosh, 1996). Liu, Erikson, and Brun (1996) purport that synaptic density and arborization of the cortical neurons are markedly reduced in the prefrontal cortex. Negative age-associated changes in prefrontal grey matter relative to white matter in participants between 18 and 81 years of age was demonstrated by Raz et al. (1993). Finally, Kawamura et al. (1993) hypothesized that white matter abnormalities may be more prevalent in frontal regions relative to other cortical areas among the oldest-old (individuals age 80 and older).

A phylogenetic hypothesis has been proposed to explain the findings of greater frontal region atrophy in areas that are evolutionarily and developmentally younger and more susceptible to age-related change (Trollor & Valenzuela, 2001). However, as Trollor and Valenzuela (2001) point out, there is a dissociation between physiological brain changes in the frontal lobe and pathological changes observed in terms of temporal lobe atrophy. Specifically, accelerated temporal lobe volume decline is a better predictor of early Alzheimer's dementia relative to frontal lobe atrophy.

There is a large body of evidence to suggest that the hippocampus is also particularly sensitive to the effects of aging. However, given the proximity of the

hippocampus to other limbic structures, measuring volumetric shrinkage proves to be rather difficult, resulting in a wide range of correlations. For instance, estimates of volumetric shrinkage tend to be variable, ranging from correlations of r = -.12 to r = - .63 (Amaral, 1999; Trollor, & Valenzuela, 2001). Decreased neuronal count in the hippocampus has been illustrated by Issa, Rowe, Gauthier, and Meany (1990). Compromised hippocampal synaptic connections have also been consistently described in the literature regarding both abnormal and normal aging (Geinisman, deToledo-Morell, & Heller, 1995).

With respect to changes in subcortical white matter, T2-weighted magnetic resonance imaging (MRI) techniques have effectively shown bright foci in the parenchyma of the brain, which are known as white matter hyperintensities (WMHs). WMHs appear in approximately 30% of older persons without dementia and are most often found in the subcortical frontal regions (Hunt et al., 1989). The increase of WMH with age can be explained in part by the demyelination that is present in the brains of older persons, which is likely to reduce axonal conductance speed. The consequence of WMHs appears to be a decrease in information processing speed and motor slowing (Trollor & Valenzuela, 2001; Ylikoski et al., 1993).

Senile plaques (SP) are one of the two neuropathological markers of Alzheimer's disease (AD). SPs are composed of a protein, beta amyloid 4, as well as astrocytes, dystrophic neuronal processes, and microglia (Kaplan & Sadock, 1998). SPs have also been shown to occur in non-demented older persons, however, they tend to be less dense and less neurotoxic relative to those associated with AD. The diffuse plaques associated with normal aging are

said to be generated by a separate biological process, which involves the cleavage of amyloid precursor protein into shorter amyloid subunits (Hof & Morrison, 1999).

The issue of plaques in the non-demented older brain is controversial in that there are those who have found SPs in brains of those who did not present with signs of dementia. Researchers have suggested that SPs increase with age and that they are inevitable if one lives long enough. Furthermore, there are individuals whose brains demonstrate cerebral amyloidosis (i.e., abnormal buildup of amyloid protein), but whose cognitive performance is equivalent to that of individuals without SPs (Trollor & Valenzuela, 2001).

Neurofibrillary tangles (NFTs), the second marker of AD, are intraneural inclusions comprised of paired helical filaments comprised of tau protein (Hof & Morrison, 1999). Among healthy older persons, NFTs accumulate with increasing age and tend to form in the entorhinal cortex, basal nucleus of Meynert, locus coeruleus, and hippocampus (Charney, Nestler, & Bunney, 1999). According to Trollor and Valenzuela (2001), NFTs do not progress to inhabit cortical neurons in nondemented persons. Conversely, NFTs and abnormally phosphorylated tau are widespread throughout all cortical areas in AD individuals. Moreover, at the cellular level, NFTs are found in the neuronal processes in AD, but almost never in normal older persons.

Interesting data regarding vascular change and the aging brain, particularly the association between capillaries and neurons, have been reported by Jucker, Battig, and Meier-Ruge (1999). These researchers purport that capillaries are more densely packed in areas with higher processing demands

and that this relative density decreases with increasing age. Moreover, it appears that the degeneration of neurons is never followed by capillary loss supplying these neurons. However, in contrast, occlusion studies have shown that damage to a single capillary can result in degeneration of neurons that are located in close proximity to the occluded or damaged capillary (see Grammas, 2000).

There is debate in the literature regarding neuronal loss and aging. This is not surprising given the fact that there is an abundance of evidence demonstrating shrinkage of the brain in both healthy older persons and individuals with AD. Long, Mouton and Jucker (1999) provide a review of the literature that states that, with the exception of the hippocampus, evidence that the number of neurons decreases with age is equivocal. However, as Trollor and Valenzuela (2001) point out, examinations of the integrity of the aging neurons can provide more relevant information. It has been suggested that synaptic density decreases with age. However, less is known about the effects of aging on axons and glial cells (Price, Hamrick, Sullivan, & Scheffe, 1998).

Proton magnetic spectroscopy studies have provided useful data on the chemical compounds of the aging brain. Proton magnetic spectroscopy is able to detect compounds such as N-acetylaspartate (NAA; an indicator of neuronal viability and density), choline containing compounds (Cho), and creatine/phosphocreatine (Cr), which allows assessment of membrane synthesis and metabolism. The results of such inquiries show that there are age-related decreases in NAA, Cho, and Cr and that the areas most implicated are the frontal lobes and hippocampus (see Trollor & Valenzuela, 2001).

There are a number of molecular theories of aging. For instance, the *calcium hypothesis* states that a notable decrease in calcium occurs with increasing age. The role of calcium includes maintaining membrane excitability, regulation of neuronal metabolism, and neurotransmitter synthesis and release. However, as one ages, alterations in calcium may include a number of deleterious consequences (Gareri, 1995). Another molecular theory concerns elevated levels of homocysteine. Homocysteine is an amino acid implicated as a risk factor for cardiovascular disease, atherosclerotic stroke, and peripheral vascular disease. Elevated levels of plasma homocysteine are said to be the result of deficiencies in vitamins B-12, B-6, and folate. Studies concerning cognition and homocysteine levels reveal that cognitive performance is reduced when homocysteine levels are high. It remains unclear, however, as to whether or not this effect is directly related to vitamin deficiency, elevated homocysteine levels, and other mediating factors (Selhub et al., 2000).

Finally, an *aging and cognition hypothesis* proposed by Mesulam (2000) paints a less bleak picture of the aging process. This author acknowledges the findings of structural, neurochemical, and molecular changes as individuals age, but also argues for a degree of plasticity in the aging brain. Mesulam (2000) hypothesized that the decrements and neurological changes associated with the aging brain may also be accompanied by an increase in efficiency of the remaining synapses. That is, as loss of neurons and synapses are a necessary aspect of early development, it is also quite conceivable that this process is necessary in the aging brain. Additionally, Mesulam (2000) provides evidence that stands in contrast to the previously discussed notions of demyelination.

Mesulum (2000) purports that cortical myelination, for example, can continue to increase into the seventh decade of life; and that dendritic branching of parahippocampal neurons can become enriched during the same period of life. Research also suggests that growth-associated protein 43, a marker for axonal growth can continue to express itself in association and limbic areas during late adulthood.

In sum, it is clear that the aging brain undergoes considerable structural, neurochemical, and morphological changes. Such changes can lead to a loss of cognitive acuity in some domains that are subserved by brain areas vulnerable to change among otherwise healthy older persons. However, there is a line of thinking that suggests that the numerous alterations associated with the aging brain are a necessary part of the developmental process and that there is a degree of plasticity associated with the normal healthy aging process (see Mesulam, 2000).

Health, Aging, and Cognition

As previously described, evidence suggests that as individuals grow older, there is an increase in complaints concerning cognitive problems as well as a notable decrease in performance on cognitive tests. Moreover, there are a number of changes that occur in the brain, making it vulnerable to neurodegenerative diseases (Mesulam, 2000). Simultaneously, the prevalence of complaints concerning physical health also increases with age (Verhaeghen & Salthouse, 1997). For instance, conditions such as cardiovascular disease and diabetes increase markedly after the age of 70 (Verhaeghen et al, 2003).

Given the coexistence of declining health, declining cognition, and the vulnerability of the aging brain, one could raise the question of whether the cognitive decline observed in “normal aging” can be attributed to poor medical health among older persons rather than aging, per se. Indeed, much is known about the etiology of dementias among older persons, however, there is less consistent information available concerning health risk factors and non-pathological cognitive decline. That is, there is less known about the extent to which systemic diseases that affect the cardiovascular, hepatic, renal, and other physiological systems alter brain structure, and have an adverse but not necessarily devastating effect on cognition (see Waldstein & Elias, 2003).

Type 2 Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from defective insulin secretion, resistance to insulin, or both (Gerozissis, 2002). Two categories of diabetes exist: Type 1 (insulin-dependent diabetes mellitus) is usually manifested in childhood or early adulthood and is the consequence of autoimmune-mediated destruction of pancreatic B-cells (Biessels et al., 2002). Those with Type 1 diabetes are eventually unable to secrete insulin. Type 2 (non-insulin dependent diabetes mellitus) is characterized by slow glucose absorption, reduced hepatic insulin sensitivity, relative reduction in insulin secretion, and increased glucagons secretion (see Awad, Gagnon, & Messier, 2004).

There are a number of risk factors for DM, such as increasing age, obesity or increased percentage of body fat, and lack of physical activity. Complications commonly associated with DM include hypertension (HTN) and

cardiovascular disease. Kidney failure, retinopathy, and peripheral and autonomic neuropathy also co-occur with DM (see Biessels et al., 2002). Finally, in addition to complications concerning the peripheral nervous system (PNS), DM has been shown to have a deleterious effect on the central nervous system (CNS).

Insulin and the Peripheral Nervous System

The role of insulin in the PNS and its relationship to DM is well-described in the literature. In brief, insulin in the PNS originates in the pancreas, and its primary role is to act as a mediator for transporting glucose into cells. Glucose provides energy to cells, thereby facilitating cell functioning. A disruption of this transport system results in compromised cell functioning (Gispen & Biessels, 2000). As previously noted, DM is essentially a disruption in the glucose transport system. That is, DM is typified by decreased secretion of insulin by the pancreas, slow glucose absorption, and by a reduced sensitivity to the presence of insulin (Awad et al., 2004).

Insulin and the Central Nervous System

There is a growing body of research examining the role of insulin in the CNS. This line of inquiry is relatively new in that much of the research regarding insulin has focused on its role in liver, muscle, and adiposte tissue functions with little consideration given to its utility in CNS functioning. In fact, it was originally thought that insulin was incapable of crossing the blood-brain barrier, thus, having no impact on the brain (see Biessels, Bravenboer, & Gispen, 2004; Schulingkamp, Pagano, Hung, & Raffia, 2000). Recent evidence has managed to refute the claim that insulin does not play a role in CNS functioning. For

instance, insulin has been shown to cross the blood brain barrier. Brain Insulin receptors (InsRbs) have been found in both human and rat brains. Further, InsRbs are widely distributed throughout the brain with marked regional variation in density. High concentrations of InsRbs have been detected in the olfactory bulb, hypothalamus, and pituitary gland. InsRbs have also been shown to be localized at the synapses where they modulate neurotransmitter release, particularly monoamines, and have been implicated in plasticity (Gerozissis, 2002). Finally, there appears to be an abundance of InsRbs in the hippocampus and neocortex, indicating a possible role for insulin in cognitive functioning (Gasparini, Netzer, Greengard, & Xu., 2002).

The role of insulin in learning/plasticity has been borne out in studies featuring streptozotocin (STZ)-diabetic rats. STZ-diabetic rats develop diabetes after receiving an injection of STZ, a toxic compound. Such inquiries examine plasticity by looking at the changes in synaptic strength and long-term potentiation (LTP) in the hippocampus of STZ-diabetic rats. Results show a deficit in the expression of NMDA-dependent receptors in the CA1 and CA3 fields of the hippocampus of STZ–diabetic rats 12 weeks following the diabetes induction (Kamal, Biessles, Urban, & Gispen, 1999).

A developmental role of brain insulin has also been identified. It has been shown that insulin activates substances thought to regulate cell growth and metabolism (Yang, Raizada, & Fellows, 1981). Moreover, insulin and InsRb levels appear to change throughout the various stages of CNS development with an increase during prenatal period, a peak during postnatal life, and then a rapid

decline, followed by a leveling out at a lower level during adulthood (Kappy & Raizada, 1982).

A neuromodulatory function of CNS insulin via a series of neurochemical cascades was proposed by Wozniak, Rydzewski, Baker, and Raizada (1993). In neuronal cells, insulin takes an inhibitory role on norepenephrine while stimulating serotonin reuptake. This increase in norepenephrine within the synaptic cleft results in the activation of the B-adrenoceptor and a subsequent increase in cyclic AMP (cAMP) within the glial cells. As a consequence of the increase of cAMP, the release of glucose from glycogen stores is enhanced, thereby providing a source of sugar to glial cells. In addition, an increase of insulin augments levels of GLUT-1 (a transporter with an affinity for glucose) which then transports glucose from glial cells to extracellular fluid. This makes available an extra source of energy to the neuronal cells. According to Schulingkamp et al. (2000), this cascade effect would require an active transport of insulin from the peripheral source (i.e., pancreas) to the CNS via a transport system or a CNS-derived source of insulin.

Brain Insulin and Glucose

Attempts at further elucidating the relationship between brain insulin and glucose have yielded a number of observations. Most notable is the suggestion that the relationship between insulin and glucose in the brain may not be as clearly defined as that of insulin and glucose in the PNS. More specifically, brain Insulin appears to exceed the purpose of mediation of glucose absorption in the brain. This assertion is based on the findings of the non-homogeneous distribution of InsRB receptors in the brain. That is, if insulin and InsRb's sole

functions were to mediate glucose transport into neurons, then one would expect a wider, more homogeneous distribution throughout the brain. In addition, there is a disparity between InsRb and insulin concentration, suggesting further that the InsRB receptor may have functions other than glucose utilization (see Shulingkamp et al., 2000).

In sum, although the precise role of brain insulin and InsRbs remains unclear, there is sufficient evidence to suggest that brain insulin and InsRbs do play an important, multifaceted role in brain functions.

Type 2 Diabetes Brain Pathology

There are a number of negative consequences produced by DM on the brain. Gispen and Biessels (2000) state that the overall pathogenesis of the DM brain can be divided into three main components: the direct neurotoxic effect of hyperglycaemia, vascular changes, and alterations in neurotrophic support.

Hyperglyceamia leads to an elevated level of glucose in the brain and as in the PNS, also leads to a polyol (sugar alcohols) pathway flux. A result of excessive activation of the polyol pathway is the conversion of the excess glucose to sorbitol and fructose. An increase in sorbitol is linked to excessive protein kinase activity (Gispen & Biessels, 2000). Protein kinase is an enzyme implicated in regulation of cell transduction by modifying cellular pathways (Farese, Sajan, & Stundaert, 2005).

Another toxic effect of hyperglycaemia is the enhanced formation of advanced glycation end-products (AGEs) in both the PNS and the brain (Gispen & Biessels, 2000). AGEs form at a constant rate among non-diabetic, healthy individuals. However, in DM pathology, the development of AGEs appears to be

accelerated due to the increased availability of sugar. According to Peppa, Uribari, and Vlassars (2003), AGEs have been implicated in almost all DM-related pathologies, such as arterosclerosis.

Consequences of accelerated AGE development include the alteration of protein structure, increased accumulation in vascular tissue, and enhanced ability to bind to AGE-binding receptors (RAGE). Binding to RAGEs can lead to endocystosis and cellular degeneration.

Finally, AGEs in DM have been implicated in the development of amyloid plaques and neurofibriliary tangles. Further, RAGE is a signal transduction receptor for amyloid protein. The association of AGE and RAGE with amyloid protein has led researchers to hypothesize that AGE in DM is a risk factor for Alzheimer's disease (Nicolls, 2004).

Accelerated Brain Aging in Type 2 Diabetes. As previously noted, cerebral atrophy, as demonstrated by enlarged ventricles and widened sulci, is one of the hallmarks of the normal aging brain (Mesulam, 2000). Of note, there is evidence to suggest that brain aging is accelerated among individuals with DM (Biessels et al., 2002). Neuroimaging techniques such as MRI and CT have shown that cerebral atrophy appears to be more pronounced in the brain of those with diabetes. There also appears to be a greater amount of white matter hyperintensities in the diabetic brain (see Biessels et al., 2002). Moreover, an increased frequency of ischemic brain lesions in diabetes have been confirmed by autopsy studies (Biessels et al., 2002). Electrophysiological studies have demonstrated that P300 latency, which is a measure of neural activity associated with memory and attentional processes, increases with age (Katada,

Sato, Ojika, & Ueda, 2004) and that this latency is greater in the diabetic brain relative to the brain of healthy controls (Gispen & Biessels, 2000; Mooradian, Perryman, Fitten, Kavonian, & Morely, 1988).

Cognitive Deficits in Type 2 Diabetes. Based on converging evidence illustrating the deleterious effect of Type 2 diabetes on the brain, it is not surprising that DM is associated with a number of cognitive deficits.

According to Awad et al. (2004), cross-sectional studies have revealed that the greatest level of impairment among individuals with DM is found on tests measuring non-contextual verbal memory (i.e., word-list recall) and processing speed (e.g., Trail Making Test Part A; Reitan, 1958). Compromised abilities have also been shown on brief dementia screening measures, such as the Mini Mental State Exam; MMSE (Folstein, Folstein, & McHugh, 1975). A smaller portion of inquiries have found deficits in both immediate and delayed recall on tests of non-contextual and contextual verbal memory. In addition, deficits in immediate and delayed recall on a test of nonverbal memory have also been revealed (Awad et al. 2004). Sub-optimal performance on tests of calculations, phonemic and category fluency, processing speed, and executive function have been demonstrated (Kanaya, Barrett-Connor, Gildergorin, & Yaffe, 2004), and others have shown decrements in motor speed (Ryan, 1988). Finally, cross-sectional studies have shown a sparing of visuospatial functioning, abstract conceptualization, and verbal and nonverbal reasoning among those with DM (Awad et al., 2004).

Impact of Type 2 Diabetes on the Oldest-Old. As previously discussed, there are a number of structural, chemical, and electrophysiological changes

associated with the healthy aging brain (see Mesulam, 2000). There is also a degree of age-related decline in certain cognitive functions (e.g., memory) among healthy older persons (Au et al., 1995; Barresi et al., 2000; Haaland et al., 2003). Researchers have purported that the changes associated with normal aging appear to be accelerated in DM. Further, it has been demonstrated that compromised ability in certain cognitive functions is a consequence of Type 2 diabetes (Awad et al., 2004; Gispen & Biessels, 2000).

Given these lines of evidence, one could argue that the structural and functional changes associated with normal aging may be exacerbated in the DM brain and that this accelerated aging brain may lead to accelerated cognitive decline with increasing age.

Medical literature is replete with studies showing that with increasing age, vulnerability to the complications of medical illness also increases (Beers & Berkow, 2000, McCall, 2005). The more serious complications associated with DM are heart disease and hypertension. Moreover, older diabetics are more vulnerable to these complications relative to younger individuals with DM. Studies have shown that among older persons, poor glycemic control is associated with increased risk of developing many of these complications (see Incalzi et al., 2002).

Although it has been demonstrated that poor glycemic control is associated with increased risk of complications of the PNS among individuals with diabetes, few studies have directly examined the effect of poor glycemic control on the CNS among older persons. However, researchers have considered the possibility that elevated levels of glucose in the brain result in

bioechmical toxicity. Mechanisms such as blood-brain barrier microvasuclar dysfunction, resulting from transient hyperglycemia; altered reuptake or synthesis of monoamine neurotransmitter due to changes in insulin availability; or both of these mechanisms operating simultaneously, have been proposed by McCall (2005).

Study Objectives

The first objective of the current study was to determine whether or not DM has a negative impact on cognition. Particular attention was paid to controlling for medical illnesses that are comorbid with DM and have been shown to be associated with impaired cognition in their own right (e.g., HTN and HD).

The second aim of the study was to determine whether or not the oldest old are particularly affected by DM. That is, will the oldest-old with diabetes demonstrate greater cognitive impairment relative to the oldest-old without DM. This research question is based on two lines of thinking. The first is the previously discussed accelerated brain aging hypothesis, which purports that the DM brain ages at a particularly rapid rate relative to healthy individuals. The second is the vulnerability hypothesis which states that the oldest old are more susceptible to the consequences of medical illness, such as cognitive impairment.

The third aim of the study was to observe whether or not a relationship between a history of poor glycemic control (i.e., chronic hyperglycemia) and cognitive impairment exists. Although research has effectively demonstrated an association between DM and cognitive impairment, few studies have directly

examined whether a history of poor glycemic control exerts a detrimental effect on cognition, particularly among older persons.

The current study will draw from the previous DM and cognition literature and examine cognitive domains that have consistently been shown to be impacted by DM, namely memory and executive functions (e.g., verbal fluency).

Clinical Implications

Recently compiled epidemiological reports indicate that DM is a serious global problem. Prevalence data show that 150 million people have been diagnosed with DM world-wide and that this figure is expected to double by the year 2025. In developed countries, the majority of individuals with diabetes will be over the age of 65 (World Health Organization [WHO], 2006). As the number of people with diabetes over the age of 65 increases, research efforts to better-understand both the medical and psychological complications associated with diabetes among an aging population are imperative.

Experiment 1: Hypotheses

Hypothesis 1. The DM Group will show significantly reduced performance compared to HC, HTN, and HTD+HD Groups on tests of immediate and delayed recall for verbal information and non-verbal information and on measures of executive functioning (e.g., Verbal Fluency).

Hypothesis 2. There will be an inverse correlation between Age and performance on tests of immediate and delayed recall for verbal information and non-verbal information and on measures of executive functioning. This hypothesis is based on previous literature showing that individuals over the age

of 80 show impairment on tests of cognition, namely, memory and executive functioning.

Hypothesis 3. There will be an interaction effect between Age and DM, such that the oldest-old (age 80 and above) with DM will be more impaired than either the young-old (age 65-79) DM patients or the oldest-old without DM. This hypothesis is based on the vulnerability and accelerated aging brain hypotheses, and the findings that the oldest-old perform worse on tests of cognition. We expect to find that the magnitude of the effect will be greater among the oldest-old.

Experiment 2: Hypotheses

Hypothesis 1. Individuals with a history of poorly maintained hemoglobin levels, indicated by elevated HbA1c levels, will perform worse on tests of memory and executive functions relative to those with well-controlled hemoglobin levels.

Hypothesis 2. There will be an interaction between HbA1c and age on cognitive measures, such that with increasing age and increasing HbA1c level there will be a decline in performance on tests of memory and executive functions.

Method

The sample for the current study consisted of participant data drawn from the database of a larger National Institute of Aging (NIA)-funded study, entitled "Culture–Fair Screening and Diagnosis of Early Dementia". A brief overview of the requirements of the Culture-Fair Screening study is provided below.

Participant Eligibility Criteria for Culture-Fair Study

Three hundred and two volunteer participants from the Geriatric Ambulatory Practice (GAP) of the Montefiore Medical Center (MMC) were consented and enrolled into the Culture-Fair study. The Principal Investigator was Ellen Grober, PhD, Department of Neurology. Eligibility criteria for the Culture-Fair study included age 65 and older, native-speakers of English or fluency in English for 30 years or more, and a score of 18 or greater on the MMSE (Folstein, Folstein & McHugh, 1975). Participants were required to have sufficient visual and auditory acuity to complete neuropsychological testing. Participants were accepted into the Culture-Fair study regardless of their medical histories. However, those with a history of psychiatric illness, such as schizophrenia or aphasia due to stroke were excluded from participation. Participants were evaluated with a set of candidate dementia screening tests and a separate set of tests to establish diagnosis.

Exclusionary Criteria for the Current Study

The general exclusionary criteria for the current study were: head trauma; history of stroke or other neurological illnesses (e.g., Parkinson's disease [PD] and Huntington's disease [HD]) known to impair cognition; a history of alcohol abuse; psychiatric disorders (e.g. schizophrenia); and individuals who were

undergoing treatment for various forms of cancer at the time of testing. Patients who received a diagnosis of dementia were also excluded from the current study (*n* = 25). A diagnosis of dementia was achieved through consensus by a neuropsychologist, geriatrician, and a geriatric psychiatrist using the DSM-IV criteria for dementia (American Psychological Association, 1994). In order to avoid diagnostic circularity, diagnosis was made without input from the patient's primary care provider or knowledge of screening tests (see Grober, Hall, McGinn, Nicholls, Stanford, et al., 2008). In terms of relevance to the current study, the scores of both the Word List and Figure Recall subtests of the CERAD (Welsh, Butters, Mohs, et al., 1994) were employed in the diagnostic procedure. However, as previously mentioned, consensus was reached without knowledge of the screening tests.

Obtaining Medical Information

As previously described, participants in the current inquiry were selected from the database of a larger study. General medical information for all participants in was previously obtained via the Clinical Impressions questionnaire, a brief checklist that provides an overview of a patient's medical history. A more detailed medical history was provided by a medical chart review, performed by a geriatrician and a neurology fellow.

Excluded Cases

Following the chart review, 100 cases were excluded from analyses based on their medical history and the final sample size for the current study was 2002. Excluded cases were as follows: those with a history of stroke (*n* = 34), Parkinson's disease (*n* = 2), psychiatric illness (*n* = 3), history of alcohol

abuse (*n* = 3), undergoing cancer treatment (*n* = 1), neurological disturbances (e.g. brain tumor, *n* = 5), MMSE of under 18 (*n* = 1), under the age of 65 (*n* = 1); missing or undetermined medical history (*n* = 17); multiple diseases and undergoing chemotherapy (*n* = 6); dementia diagnosis (*n* = 25); ETOH abuse (*n* = 2). There were no cases of patients with head trauma or Huntington's disease.

Participant Inclusion Criteria for Current Study

The patients selected for the current study met the inclusion criteria. Below are the inclusion and exclusion criteria specific for each of the medical groups.

Type 2 Diabetes (DM) Group. The data from 46 participants with a diagnosis of DM were selected from the Culture-Fair database and analyzed in the current study. The eligibility criteria for inclusion into the DM group consisted of a diagnosis of Type 2 diabetes. Due to the high comorbidity of HTN and HD with diabetes, diabetic participants who also presented with HD and/or HTN were included.

The rationale for including individuals with HTN and HD in the medical illness control groups was based on findings that both of these health issues are highly comorbid with DM. Moreover, in independent reviews of the literature, Awad et al. (2004) and Biessels et al. (2002) asserted that a well-controlled DM and cognition study should include the same number of controls with medical issues as those with DM.

Hypertension (HTN) Group. The data of 68 Hypertensives were selected for the current study. The inclusion criterion was a history of HTN.

Hypertension and Heart Disease (HTN+HD) Group. The data of 53 individuals with a diagnosis of both HTN and HD were selected for the current study. It is important to note that HTN is a disease that is highly comorbid among those with HD. Indeed, all of the patients in the current study with a form of heart disease also had HTN.

Healthy Control (HC) Group. The data of 35 healthy individuals were selected for the current study. The exclusionary criteria for the HC group included a diagnosis of Type 1 or Type 2 DM, HTN, or HD.

Neuropsychological Assessment Procedures

All participants in the Culture-Fair study database had undergone a brief telephone interview, a recruitment interview, and neuropsychological testing. The telephone interview served as an introduction to the study and was conducted 1 to 2 days before the patient's medical appointment at the Geriatric Ambulatory Practice (GAP). Informed consent was obtained, and a recruitment interview was administered.

The recruitment interview consisted of a series of questions to obtain demographic/socio-economic information, activities of daily living information, and attitudes towards health. The MMSE (Folstein et al., 1975), a test of global cognitive functioning, was also administered. Scores on the MMSE range from 0 to 30 (Folstein et al., 1975), and a score of 18 or greater determined eligibility.

The neuropsychological testing session was conducted an average of 3 to 6 months following the recruitment interview. The neuropsychological test battery assessed cognitive domains including memory for verbal and non verbal

information, visuospatial skills, and executive functions. All interviews and tests were conducted by members of the Culture-Fair study research staff.

Screening Measures

The Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) was administered at the recruitment interview to assess level of cognitive functioning. The MMSE is a widely used test that surveys functioning in various cognitive domains, including short-term memory, calculations, attention, orientation, and visuospatial construction. The MMSE takes approximately 10 minutes to administer and is comprised of 30 items, with a possible score of 30.

American Version of the National Adult Reading test (AMNART; Grober & Sliwinski, 1991). The AMNART consists of 45 words that cannot be pronounced by sounding them out (e.g., “depot” and “ache”). The number of correctly read AMNART words provides an estimate of premorbid verbal intelligence. Premorbid Verbal intelligence (VIQ) was computed with the following formula: VIQ=118.56 - .88(# of errors) + 0.56 (years of education). In addition to VIQ, literacy was also assessed by the AMNART. Specifically, the number of words correctly read out of 45 was employed to assess Literacy.

Geriatric Depression Scale (GDS; Sheifjkh, & Yesavage, 1986) Depression was assessed via the Geriatric Depression Scale (GDS). The GDS is geared specifically towards older persons and omits items dealing with sexuality, and feelings of guilt. The GDS consists of 15 questions and follows a yes/no response format, thereby, minimizing cognitive demands (Spreen & Strauss, 1998).

Neuropsychological Tests

The Free and Cued Selective Reminding Test (FCSRT; Grober & Buschke, 1987).

FCSRT: Picture Naming. The naming procedure of the Free and Cued Selective Reminding Test (see description below) follows the format of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and is a measure of the integrity of semantic representation and retrieval ability. The naming task consists of 16 simple line drawings of common objects (e.g., grapes and canoe). The purpose was to ensure that the participant could retrieve the names of the items used in the FCSRT.

The participants were presented with the pictures, one at a time, and asked to name each item. Semantic and phonemic cues were provided for items that were not named spontaneously. For example, if the participant did not spontaneously name grapes when presented with the picture, he/she was provided with the semantic cue (i.e., type of fruit). In the event that the participant was still unable to name grapes after receiving the semantic cue, he/she was then provided with a phonemic cue (e.g., starts with gr).

FCSRT: Verbal Memory Test is a test of memory that shows the presence of memory impairment that is not caused by other cognitive impairment, such as deficits in attention and processing speed. Attention and cognitive processing are controlled by having the participant search for the to-be-remembered items in response to cues (Grober, Lipton, Hall, & Crystal 2000; Grober, & Kawas, 1997).

The FCSRT began with a study procedure in which subjects were presented with a total of 16 items, 4 at a time. The items were presented on

cards arranged in quadrants, one item per quadrant. The subjects were asked to search the card containing the 4 items (e.g., grapes, vest, train, and candle) for an item that goes with a unique category cue (e.g., fruit). After all 4 items were identified, immediate cued recall of just those 4 items was tested. The search was performed again for items not retrieved by cued recall. The search procedure was continued until all 16 items were identified and retrieved in immediate cued recall. The study procedure was followed by 3 trials of recall, each consisting of free recall followed by cued recall for items not retrieved by free recall. Items not retrieved by cued recall were re-presented (e.g., the fruit was grapes). There were 20 seconds of interference (counting backwards) between trials. The sum of free and cued recall on each trial is called total recall. There is a possible score of 16 (sum of free recall and cued recall) for each trial for a total recall of 48.

Verbal Fluency-category (Rosen, 1980). The categories test assesses the capacity for spontaneously generating exemplars of items from semantic categories (e.g., animals, fruits, or vegetables). The participant was asked to generate as many exemplars from each of the categories in 60 seconds. The score consists of the total number of items given in 60 seconds minus any intrusions from other categories and perseverations. The number of correct items produced at specific time intervals (e.g.,15, 30 and 45 seconds) are recorded.

Consortium to Establish a Registry for Alzheimer's disease (CERAD) – Word List (WL). (Welsh, Butters, Mohs, et al., 1994). On the CERAD- WL, the participant is presented with 10 unrelated words (e.g., grass, engine). The

participant was required to read the words aloud, one at a time. Following the presentation of all 10 words, the participant was required to immediately recall the words in 90 seconds. There were 3 trials in total. The participant was then required to recall the word list once again 10 minutes later without re-presentation of the words. Delayed recall (CERAD-WL- delayed) was found to be the best overall discriminatory measure in distinguishing mild AD cases from controls (Welsh et al., 1990).

The CERAD Figure Recall Test is a test of constructional ability that requires the participant to copy four geometric shapes (circle, a diamond, overlapping rectangles, and a 3-dimensional cube). The CERAD figure recall test requires the participant to recall the 4 geometric figures that were copied earlier. A score of 2 or less on figure recall (20% retention) is considered impaired.

Clock Drawing (Freeman, Leach, Kaplan, Winocur, 1994). The Clock Drawing test was used to assess unilateral visuospatial inattention. The procedure requires the participant to draw a clock free-hand. Specifically, the participant is told to draw a circle, insert the numbers, and then to set the clock to read 20 minutes past 8. A maximum of 15 points can be obtained on the free-hand clock drawing. One point is given if certain criteria are met, such as numbers are in correct order and position, hour and minute hands are in the correct location and proportion, and the participant is able to draw the contour of the circle. For the second clock drawing trial, the participant was provided with a pre-drawn circle and was told to insert numbers and set the clock to read 10 minutes after 11. The maximum score for this test is 12. The criteria are the

same for the freehand task except there are no points awarded for quality of the circle. The final task requires the participant to copy a clock. There are a maximum of 15 points.

The neuropsychological tests utilized in the current study have been established in the literature as being reliable measures of their respective cognitive domains. Verbal memory was assessed by both the CERAD and the FCSRT. The CERAD was used to measure both immediate word list memory and delayed recall. The FCSRT also assess verbal memory, though there is a notable distinction between the tests. As previously described, the FCSRT controls for factors, such as inattention and inefficient cognitive functioning, that could have a negative influence on memory performance among the elderly. In contrast, the CERAD-WL does not control for possible deficits in attention and cognitive processing.

Visuospatial memory was evaluated with the Figure recall portion of the CERAD. Executive functions were evaluated with the Verbal Fluency-category test and Clock Drawing, a measure of planning ability.

Data Preparation

Removal of Outliers

The first step in the data analysis procedure was to identify and remove any significant outliers in the dataset in order to reduce the possibility of committing a Type I or Type II error. Histograms were employed to visually determine whether or not the data for each cognitive test were normally distributed. Box Plots were then utilized to identify univariate outliers. Following outlier identification, the data were then treated to the Winsorized method. The

Winsorized method is a robust statistical method that involves the temporary censoring of significant outliers (i.e. 3 standard deviations). Means and standard deviations on the new data were obtained and the outliers were replaced with the adjacent extreme score which is typically 2 standard deviations from the mean. Descriptive statistics were obtained and box plots and histograms were generated once again in order to confirm that the outliers were longer present.

Medical Group Demographic Analyses

In order to limit the effects of confounds such as race, gender, and medication use, chi-square tests were performed to assure that the potentially confounding variables were equally distributed across the four 4 groups.

Possible confounds such as age, years of education, and geriatric depression scores were each analyzed by a one-way ANOVA. Categorical screening variables were examined with chi-square and continuous variables were evaluated with a one-way ANOVA or Kruskal Wallis. Table 1 shows demographic data (e.g., sex, race, age, years of education). Table 2 shows screening measures by medical group (e.g., MMSE, GDS, & AMNART).

Experiment 1: Study Design and Statistical Procedure

Study Design

There were four medical diagnosis groups under study. All groups met the previously described inclusion and exclusion criteria. The referent group consisted of 46 individuals with DM and comorbid medical conditions (e.g., HTN and heart disease [HD]). There were two medical illness control groups (HTN, HTN+HD) and a HC group. The HTN group consisted of 68 individuals without a diagnosis of DM but who were undergoing treatment for HTN at the time of

testing. The HTN+HD group consisted of 53 individuals being treated for HTN who had a history of heart disease such as atrial fibrillation (AFIB) or myocardial infarction (MI). The HC group consisted of 35 healthy individuals who were free of DM, HTN, HD, and of the previously mentioned exclusion criteria.

Statistical Procedure

The first hypothesis sought to examine whether or not individuals with Type 2 DM performed worse on tests of cognition utilized in the current study relative to healthy controls and the medical illness control groups. For the second hypothesis, we expected to find that increasing age was associated with poor performance on tests of cognition. The third hypothesis expected to find an age by group interaction with the strongest magnitude of the effect for the DM group.

The independent variables consisted of medical group (DM, HTN, HTN+HD, and HC), which was entered as a fixed variable, and age, which was entered as a continuous, random variable for each test. Entering age as a continuous variable is a more sensitive approach that has been shown to be able to detect relatively small differences when they do exist, particularly when examining the interaction effects with a relatively small sample size (Cohen, 1983).

Race and premorbid verbal IQ were not equal across groups (see demographic variable and neuropsychological test analyses below). As a result, race and IQ were treated as possible covariates. Moreover, race and IQ have been shown in the literature to influence performance on neuropsychological tests. Schwartz, Glass, Bolla, Stewart, Glass et al. (2004) discuss the effects of

Race on tests of memory and executive functions. Manly et al. (2002) suggest that literacy is a moderator of performance on tests of cognition.

In order to reduce the possibility of committing a Type II error associated with excessive or incorrect use of covariates, the data were run without covariates by way of a 2-way Analysis of Variance (ANOVA), with age and Medical Group as independent variables and test score as the dependent variable. Race was then covaried first to determine whether or not it changed the initial model. In cases where race was not significant or did not change the initial outcome, race was not used as a covariate. IQ was then covaried and in cases where IQ did not alter the initial outcome, it was not used as a covariate. When either race, IQ, or both Race and IQ were found to be significant covariates, the data were analyzed using an Analysis of Covariance (ANCOVA). This procedure was conducted on each test utilized Experiment 1.

Regarding interaction effects, because an interaction with four groups would yield results that would be difficult to interpret, separate analyses were conducted. A new classification was created which paired each medical illness group to the HC group. A group by age interaction term was then created and the following interactions were examined: (DM vs. HC) x age; (HTN vs. HC) x age; and (HTN+HD) vs. HC x age.

For the tests that were not normally distributed, non-parametric tests were used. A Kruskal-Wallis, non-parametric version of an ANOVA, was conducted on the ranked scores of the four groups (e.g., medical group). A Mann-Whitney test was employed to evaluate ranked scores of two groups (e.g., race).

When a significant main effect of group was found, planned comparisons were conducted comparing the performance of the DM, HTN+ HD, and HTN, group against that of HCs. Independent *t*-tests were employed to further assess differences among the DM and medical illness control groups.

When a significant main effect of age was found, the data were dichotomized using age 80 as a cut-point, such that age 80 and above was considered the oldest-old and 79 and below was considered the young-old. Independent samples *t*- tests were used to test the oldest-old hypothesis.

A significant race covariate was examined with an independent group *t*-test. Significant premorbid IQ covariate was examined by establishing the median score as a cut-off point and conducting an independent groups *t*- test on the scores above and below the median.

For significant non-normally distributed test results (e.g., Kruskal-Wallis), box-plots were used to determine where the greatest difference had occurred based on median values. The Mann-Whitney U-test, a non-parametric version of the *t*-test, was used to follow up box-plot findings. All data were analyzed using SPSS V. 11, and the probability level was set at .05.

Medical Group Demographic Analysis Results

Medical Group Demographics Overview

DM. The DM group contained a total of 46 participants: 10 men (22%) and 36 women (78%). The age of the diabetic group ranged between 66 and 99 (M = 76.91, SD = 7.23). The racial distribution for the DM group was 16 White (34%) and 30 Black (65%) participants. Years of education for the DM group ranged between 5 and 19 years (M = 12.35, SD = 2.82). Estimated premorbid

VIQ ranged from 80 to 127 (*M* = 104.52, *SD* =12.79). GDS score ranged from 0 to 11 (*M* = 3.02, *SD* = 2.67).

HTN. The hypertension only group consisted of 68 participants; 7 men (10%) and 61 women (90%). The age of the group ranged from 65 to 97 (*M* = 78, SD = 7.1). The racial distribution of the group was 29 White (43%) and 39 Black (57%) participants. Years of education ranged from 5 to 18 (*M* = 12.99. *SD* = 3.41). Estimated premorbid VIQ ranged from 80 to 129 (*M* = 110.13, *SD* = 13.7). The GDS scores ranged from 0 to 11 (*M* = 2.49, *SD* = 2.71).

HTN+HD. The hypertension and HD group consisted of 53 participants: 11 men (14%) and 42 women (86%). The age of the group ranged between 66 and 92 (*M* = 79, SD = 5.9). There were 26 White (49%) and 27 Black (51%) participants. Years of education ranged from 0 to 18 (*M* = 12.83 *SD* = 3.45) and estimated premorbid VIQ ranged from 81 to 129 (*M* = 111.37, *SD* = 12.32). The GDS scores ranged from 0 to 8 (*M* = 2.64, *SD* = 2.18).

HC. The healthy control group was comprised of 35 participants: 5 men (14%) and 30 women (86%). The age of the group ranged between 66 and 92 (*M* = 77.25, *SD* = 7.53). There were 23 White (66%) and 12 Black (34%) participants. Years of education ranged between 6 and 19 (*M* = 12.98, *SD* = 2.93). Estimated premorbid VIQ ranged from 88 to 128 (*M* = 112.99, *SD* = 11.17). The GDS score of the group ranged between 0 and 6 (*M* = 2.63, *SD* = 1.88).

Demographic Variables x Medical Group

Results for the demographic variables are presented in Table 1.

Race x Medical Group. The results of a 2 x 4 chi-square test revealed that there was a significant relationship between race and medical group χ^2 (3, N = 202) = 8.27, p = .04. There were significantly more African Americans in the DM group and more White participants in the HC groups than expected.

Gender x Medical Group. A 2 X 4 chi-square test was conducted to examine the frequency of men versus women among the 4 groups. Results show that there was no significant difference in the number of men and women among the medical groups, χ^2 (3, N = 202) = 3.66, p = .30.

Handedness x Medical Group. A 2 x 4 chi-square analysis was conducted on handedness (right-handed, left-handed, and ambidextrous). There was no significant difference among the groups in handedness, χ^2 (3, N = 202) = 2.05, p = .90.

Age x Medical Group. A one-way ANOVA was conducted to show whether or not a relationship between age and group existed. Results revealed no significant difference in age across the four groups, F(3, 201) = 0.53, p = .66.

Years of Education x Medical Group. A one-way ANOVA was conducted to examine the relationship between years of education and medical diagnosis. Results revealed that there was no significant difference in the level of education among the four groups, F(3, 201) = 0.39, p = .76.

In sum, there were no significant difference between the medical groups in the following demographic variables: sex, age, years of education, handedness, and medication use. However, there was a significant difference in

race such that there were more African Americans in the DM group and more White participants in the HC group.

Screening Measures by Medical Group.

Results for screening measures data are presented in Table 2.

MMSE x Medical Group. A one-way ANOVA was conducted to determine whether or not a difference among the four groups existed on the MMSE scores. There was no significant difference among the groups on the MMSE, $F(3, 201) = 1.72$, $p = .16$.

GDS x Medical Group. A one-way ANOVA was conducted to determine whether or not the four groups differed on GDS scores. Results showed that there was no significant difference in the depressive symtpoms among the groups $F(3, 201) = 0.49$, $p = .68$.

Premorbid Verbal IQ (VIQ) x Medical Group. A one–way ANOVA was conducted to determine whether there were differences in estimated premorbid VIQ among the four groups. A significant difference in estimated premorbid VIQ was found $F(3, 201) = 2.9$ $p = .03$, such that the DM group had lower IQ scores relative to the controls, $p = .00$ and the HD+HTN group, $p = .00$.

Picture Naming x Medical Group. A Kruskal-Wallis test was conducted to examine differences in naming ability among the four groups. No significant difference was found, $H(3) = 0.21$, $p = .97$

In sum, there was no significant difference among the medical groups in terms of mental status, picture naming scores, or depressive symptoms. However, a significant difference was revealed for estimated VIQ, such that the

DM group had a significantly lower estimated VIQ score relative to the HCs and the HTN+HD group.

Results

Experiment 1 results

Memory

FCSRT- Free Recall. Since both Race and VIQ were not evenly distributed across the 4 medical groups, an ANCOVA was conducted using Race and VIQ as covariates to assure that they were not influencing the outcome. Results indicated that there was no significant effect of Race, $F(1,167) = 2.59$, $p = .10$, or VIQ, $F(1,167) = 1.94$, $p = .16$.

A 2-way ANOVA was conducted using the between-subjects variables of Age and Medical Group on the FCSRT free recall scores. Results revealed a significant main effect of Medical Group, $F(3, 200) = 4.90$, $p = .00$ (Table 3). Results of the planned comparisons on group revealed a significant difference between the DM group and HC ($p = .01$, $r = .13$), such that the DM group ($M = 28.02$, $SD = 7.90$) performed significantly worse than HC ($M = 30.54$, $SD = 6.98$). The HTN+HD group ($M = 26.00$, $SD = 7.73$) were also significantly compromised relative to the controls ($p = .00$, $r = .25$). There was no statistically significant difference ($p = .08$) between the HTN group ($M = 29.70$, SD =6.39) and HC ($M = 30.54$, $SD = 6.98$; Table 4).

Independent samples *t*-tests were conducted to further investigate differences among the 3 medical illness groups (Table 4). Specifically, we wanted to evaluate the difference among the HTN+HD, HTN, and DM. Results showed a significant difference between the HTN and HTN+HD groups, $t(118) = 2.8$, $p = .00$, $r = .13$. The HTN + HD group's performance ($M = 26.00$, $SD = 7.73$) was significantly worse than that of the HTN group ($M = 29.70$, $SD = 6.39$).

There was no significant difference (p = .20) between the DM and HTN+ HD group, nor was there a significant difference between DM and HTN group (p = .21). Figure 1 depicts Group differences.

A main effect of Age was also found F (29, 200) = 2.01, p = 0.00 (Table 3). An independent sample t-test revealed a significant difference (Table 5). The oldest-old (M = 25.91, SD = 7.94) performed significantly worse than the young-old group (M = 30.09 SD = 6.52), t(1, 200) = 4.05, p = .00 (see Figure 2).

There was no significant interaction between DM and Age on the FCSRT, F(15, 81) =0.65, p = .81. Similarly, there was no significant interaction between HTN and Age, F(17. 100) = .64, p = 0.84 or between HTN+HD and Age, F= (16, 88) = 0.33, p = .99 (Table 3).

In summary, analysis of the FCSRT data demonstrated that the covariates of Race and VIQ were not significant. Data revealed an effect of group, with the DM and HTN+HD groups performing worse than controls. Further, an effect of Age was shown, such that the oldest-old recalled fewer items than the young-old. There was no Age by Group interaction.

CERAD-WL. The results revealed no effect of Race (p = .49). When premorbid VIQ was covaried, the data revealed an effect of estimated premorbid VIQ, F(1, 164) = 7.76, p = .00. Estimated premorbid IQ was further analyzed by using the median score of 111.00 as a cut-point. A independent samples t-tests reveal that those with premorbid VIQ of 111.00 and over recalled significantly more words than those with VIQ scores below 111.00, t(195) = 2.47, p = .01, r = .11.

The was no main effect of Group $F(3,164) = 2.08$, $p = .10$. A significant main effect of Age was revealed after controlling for VIQ, $F(28.164) = 2.94$, $p = .00$. An independent groups *t*-test revealed that the oldest-old ($M = 16.90$, $SD = 3.96$) performed significantly worse that the young-old ($M = 19.91$ $SD = 4.03$), $t(195) = 5.10$, $p = .00$, $r = .44$ (Table 5). Figure 3 shows mean recall scores for the two Age Groups.

There were no significant interactions between DM and Age $F(15, 79) = 0.79$, $p = 0.67$; HTN and Age $F(17, 98) = .094$, $p = .53$; or HTN+HD and Age $F(16, 87) = 0.50$, $p = .93$. Main effects and interaction data are presented in Table 6.

In summary, the CERAD-WL data revealed that the covariate VIQ was significant, such that those who had a VIQ score above 111.00 recalled significantly more words than those with VIQ scores below the median. There was no effect of group. However, an effect of age was illustrated, such that the oldest-old recalled fewer words than the young old. Finally, there was no interaction between Age and Group.

CERAD – WL (delayed recall). Race and VIQ were entered as covariates. The results revealed no effect of Race ($p = .59$). A significant effect of VIQ was illustrated $F(1, 164) = 15.5$, $p = .00$. Independent *t*-test using the median VIQ (111.00) as a cut-off point revealed that the individuals with a VIQ above 111.00 recalled significantly more words ($M = 6.10$, $SD = 2.28$) than those with a VIQ score below 111.00 ($M = 5.14$, $SD = 2.15$), $t(195) = 3.02$, $p = .00$, $r = .21$. There was no significant main effect of Group $F(3, 164) = 0.88$, $p = .44$.

An effect of Age was revealed after controlling for VIQ $F(28, 164) = 2.26$, $p = .00$ .The oldest-old ($M = 4.77$, $SD = 2.41$) recalled significantly fewer words than the young-old group ($M = 6.16$, $SD = 2.01$), $t(195) = 4.36$, $p = .00$, $r = .31$ (Table 5). Figure 4 shows mean recall for the 2 age groups.

There was no significant interaction between DM and Age $F(15, 79) = 0.85$, $p = 0.61$; HTN and Age $F(17, 98) = 0.74$, $p = .75$; or HTN+HD and Age $F(16, 87) = 0.38$, $p = .98$. Main effect and interaction data are presented in Table 7.

Overall, the data revealed that those with those who had a VIQ score above the median of 111.00 recalled significantly more words than those with VIQ scores below the median. There was no effect of Group. However, an effect of Age was illustrated, such that the oldest-old recalled fewer words than the young-old. There were no interaction between Age and Group.

CERAD-Figure Recall. Due to the non-normal distribution of the CERAD-Figure Recall scores, a Kruskal Wallis analysis on ranked scores was employed to examine whether or not a difference in performance among the medical groups on the CERAD Figure Recall existed.

A significant difference among the Medical Groups was revealed (H) (3) = 7.65, $p = .05$ (Table 8). Mann-Whitney tests were used to follow up this finding. A boxplot of the data was utilized to determine where the greatest differences in the ranks lie. Results revealed that the HC had a higher rank relative to the 3 medical illness groups. Thus, the ranking of HC was used as a point of comparison for the three Medical Groups. A Kruskal Wallis test was conducted comparing the performance of the DM, HTN, and HTN+HD groups against the

HC group. Results showed that the DM group (Mean rank = 33) performed worse relative to the HCs (Mean rank = 45), $p = .02$. The HTN+HDs (Mean rank = 39) performed worse than HCs (Mean rank = 51), $p = .02$. There was no difference between the HTN (Mean rank = 47) and HC groups (Mean rank = 54), $p = .26$.

A Mann–Whitney test was conducted on Age Groups (young-old and oldest-old). The ranked data (Table 5) revealed that the oldest-old (*Mdn* = 5) performed significantly worse on the CERAD Figure (recall) test in comparison to the young-old (*Mdn* = 7), $U = 2778.00$, $p = .00$, and that the effect size fell within the medium range, $U = 3284.50$, $r = .34$ (Table 9). Figure 5 shows mean recall for the two Age Groups (.young-old and oldest-old)

Both the DM and HTN+HD groups performed worse than HCs on the CERAD Figure recall test. The data revealed that the oldest-old recalled fewer items than the young-old.

With regard to memory, the data revealed that both the DM and HTN+HD group were impaired on the FCSRT relative to the HC group. Further, the oldest-old recalled significantly fewer items than the young-old. With regard to the CERAD-WL and CERAD–WL delayed recall, when estimated VIQ was controlled for here was no difference among the Medical Groups in the ability to recall a list of words. An effect of estimated VIQ also emerged, showing that individuals above the median recalled more words than those below the median. An analysis of the Age effect showed that the oldest-old recalled fewer words than the young-old on both CERAD-WL tests. In terms of the CERAD Figure-recall, both the DM and HTN+HD groups performed worse than HCs. Further,

there was no Age by Medical Group interaction on any of the tests employed in the current study.

Executive Functions

Verbal Fluency-category. Race and estimated VIQ were used as covariates. Results revealed that Race was not significant $F(1, 164) = 0.20$, $p = .65$., while estimated VIQ was significant $F(1, 164) = 62.92$, $p = .00$. An independent samples *t*-test revealed that those with an estimated VIQ above the median generated more words ($M = 41.14$, $SD = 10.16$) than those with an estimated VIQ below the median ($M = 32.07$, $SD = 8.08$), $t(196) = 6.9$, $p = .00$. There was no effect of Group $F(3, 164) = 0.58$, $p = .62$. There was no effect of Age though a trend was revealed $F(28, 165) = 1.5$, $p = .06$.

There were no interactions between DM and Age $F(15, 78) = 1.6$, $p = .10$; HTN and Age $F(17, 100) = 1.10$, $p = .32$; and HTN+HD and Age $F(16, 87) = 0.64$, $p = .83$. Main effect and interaction data are presented in Table 10.

While controlling for both Race and estimated VIQ, the data showed that the covariate VIQ was significant, such that those above the median generated more words than those below the median. There was no effect of Group nor was there an effect of Age.

Clock Drawing. A Kruskal-Wallis test revealed no significant difference among the four medical groups, $H(3) = 0.81$, $p = .87$ (see Table 11).

A Mann-Whitney U test was conducted on Age Group. A significant difference (see Table 12) emerged, such that the oldest-old performed worse than the young-old group, $U = 3304.00$, $p = .00$, $r = .26$. A Mann-Whitney U test

revealed that individuals with a VIQ below 111 ranked lower (78.59) than individuals with a VIQ greater than 111 (113.68), $U = 2022.00$, $p = .00$

With regards to tests of executive functioning, there were no group differences on verbal fluency or clock drawing. Premorbid VIQ was shown to influence performance on the verbal fluency and clock drawing tests, with those above the median performing better than those below the median. For Age, a significant difference between the oldest-old and young-old emerged on the Clock Drawing test. No Age by Group interaction was revealed on the Verbal Fluency test.

In sum, the results of Experiment 1 revealed that with respect to memory, both the DM and HTN+HD group were impaired on the FCSRT relative to the HC and HTN groups. However, there were no group differences on the CERAD-WL or the CERAD-WL- delayed recall. In terms of the CERAD Figure Recall test, the DM and HTN+HD group performed worse than the HCs. With regard to Age, the oldest-old performed significantly worse than the young-old on the FCSRT, CERAL-WL, CERAD-WL delayed recall, and CERAD Figure recall. No Age by Group interaction was observed.

Analyses of executive functions revealed that there was no difference among the Groups on Verbal Fluency-category or on the Clock Drawing test. In terms of Age, the oldest-old performed significantly worse than the young-old on the Clock Drawing test but there was no difference between the oldest-old and young- old on the Verbal Fluency test. Finally, VIQ was shown to be significant in verbal fluency and clock drawing capabilities. No Age by Group interactions emerged.

Experiment 2: Study Design and Statistical Procedure

Study design. We expected to find that individuals with a history of poorly maintained hemoglobin levels, indicated by elevated HbA1c, would perform worse on tests of memory and executive functions relative to individuals with well-controlled hemoglobin levels. Further, we expected to find an inverse relationship between Age and performance. We also expected to find an interaction between HbA1c and Age on measures of cognition.

An HbA1c level of 7 has been established in the medical literature as the dividing point between compliant and non-compliant diabetics (Kennedy, Herman, Strange, & Harris, 2006). An HbA1c level of ≤ 7 indicates compliance with medical treatment and adherence to proper diet. Conversely, an HbA1c level of > 7 is an indicator of non-compliance with the prescribed treatment regimen.

Although HbA1c of > 7 is recognized as an indicator of non-compliance in medicine, it was unclear as to whether or not the HbA1c > 7 score was suitable as a dividing point in psychological research. That is, it is possible that cognitive impairment may be associated with an HbA1c level higher or lower than 7. Indeed, the normal level of HbA1c in a non-diabetic is 3.5, whereas for a compliant diabetic, the level is 5. Thus, for the current study HbA1c level was evaluated as a continuous variable.

HbA1c was recorded for each DM patient at four time intervals: at the time of testing and at 6, 18, and 24 months prior to testing. An average HbA1c level was calculated and used in the current analysis.

Statistical Procedure. A hierarchical multiple regression analysis was conducted on each normally distributed test utilized in the current study. The first step was to evaluate the effect of the covariates Race and literacy on each test of cognition. Analysis of the covariates was conducted by using simple regressions for each of the tests of cognition. Because there were significantly more Black participants in the DM group relative to White participants and because Race has been shown to be associated with performance on tests of cognition, Race was entered into a regression model first. If Race was shown to be significant, literacy was then entered into the model in order to determine if the race effects were being driven by literacy (see Manly, Schupf, Tang, & Stern, 2005). If Race was not significant, a simple regression was conducted with literacy to determine whether or not it was significantly associated with the dependent variable. Thus, if one or both of the covariates were found to be significant, they were utilized in the model. Conversely, non-significant covariates were not placed in the model.

The predictor variables under study were Age, HbA1c, and the interaction between HbA1c and Age. Age, HbA1c, and the covariate VIQ were centered by subtracting the mean of the variable from the variable score. Centering predictor variables is recommended when examining interactions in regression analysis as it reduces the possibility of multicolinearity effects (Fields, 2005). An interaction term was created by multiplying the centered values of Age and HbA1c.

A hierarchical multiple regression was conducted on each of the following measures of cognition: FCSRT, CERAD-WL, CERAD-WL delayed, CERAD

Figure recall, and Verbal Fluency. Significant covariates were entered into the model first followed by Age, HbA1c, and the HbA1c by Age interaction.

Post hoc analyses were conducted on significant categorical variables (e.g., Race) via an independent samples *t*-test. The procedure for post hoc tests on the interaction of two continuous variables is outlined in Aiken and West (1991). This procedure involves the computation of two conditional group variables for intelligence level, one in which the low HbA1c group is defined as those with HbA1c levels lower than 1 *SD* below the mean and one in which the high HbA1c group is defined as those with HbA1c levels above 1 *SD* from the mean. One regression generated the slope for the lower intelligence group, and a second regression generated the slope for the higher intelligence group. These slopes were then used to plot regression lines on the basis of two equations, substituting high (1 *SD* above the mean) and low (1 *SD* below the mean) values for HbA1c scores in each equation.

Experiment 2 results

Memory

FCSRT – Free Recall. Race (β = 0.28, $p = .06$) and literacy (β = -0.09, $p = .57$) were not found to be significant predictors of FCSRT and were not entered into the model as covariates. Hierarchical regression analyses were conducted to examine the impact of Age, HbA1c, and the Age by HbA1c interaction on free recall ability. The regression analysis revealed no significant effect of Age, β = -0.10, $p = .55$; $R^2 = 0.04$, $F(1, 43) = 1.58$, $p = .21$. There was no effect of HbA1c, β = -0.27, $p = .07$; $R^2 = 0.10$, $F(2, 43) = 2.39$, $p = .10$.

However, a trend towards an Age by HbA1c interaction was revealed β = -0.31, p = .06; R^2 = 0.18, $F(3, 43) = 2.94$, p = .04 (Table 13).

In summary, neither age nor HbA1c predicted performance on the FCSRT. Additionally, there was no significant interaction between Age and HbA1c. However, the data suggested a trend towards an Age by HbA1c interaction, such that participants with low HbA1c recalled fewer items with increasing age. Participants with high levels of HbA1c were comparable their counterparts with low HbA1c between the ages of 65 to 70 but improved with increasing age, declining gradually after age 80. Moreover, the older participants with high HbA1c recalled more words than their comparable age cohorts with low HbA1c.

CERAD- WL Race (β = 0.39 p = .04) was found to be a significant predictor of performance and was entered as a covariate after controlling for literacy (β = 0.05 p = .78). Hierarchical regression analyses were conducted to examine the impact of Age, HbA1c, and an Age by HbA1c interaction on word list learning capabilities while controlling for Race. Regression analyses revealed that Race was significantly associated with recall, β = 0.35 p = .017; R^2 = 0.10, F (1, 43) = 5.12, p = .02, with an adjusted R^2 value of 0.08. Independent samples t-test revealed that the Black participants recalled significantly more words (M = 19.57, SD = 3.78) than their White cohorts (M = 16.87, SD = 3.82), $t(42) = 2.26$, p = .02. Age did not significantly predict the number of words recalled, however, there was a trend towards an Age contribution to the amount of variance in the model, β = -0.02, p = .12; R^2 = 0.00, F (2, 43) = 2.90, p = .06. HbA1c significantly predicted recall scores, such that with increasing HbA1c

levels, there was a decrease in the number of words recalled, β = -0.38, p = .00; R^2 = 0.25, F (2, 43) = 4.65, p = .00, with an adjusted R^2 value of 0.20 (Figure 6). A significant Age by HbA1c interaction was revealed β = 0.33, p = .02; R^2 = 0.34, F (3, 43) = 4.65, p = .00 (Table 14). Interaction data are illustrated in Figure 7.

The data revealed that Race was a significant predictor of CERAD-WL with Black participants recalling significantly more words than the White participants. Age was not shown to be a predictor of recall. However, HbA1c was shown to be a predictor. Further, a positive Age by HbA1c interaction was also shown.

CERAD – WL (delayed recall). Race (β = 0.14, p = .36) and Literacy (β = -0.04, p = .79) were not found to be significant predictors of delayed verbal recall and were not entered into the model as covariates. Hierarchical regression analyses were conducted to examine the impact of Age, HbA1c, and the Age by HbA1c interaction on delayed verbal recall. Regression analyses revealed that Age did not significantly predict the number of words recalled, β = 0.05, p = .75; R^2 = 0.00, F (1, 42) = 0.16, p = .69. HbA1c significantly predicted recall scores, such that with increasing HbA1c levels, there was a decrease in the number of words recalled, β = -0.43, p = 0.00; R^2 = 0.17, F (2, 41) = 4.43, p = .01 (Figure 8). A significant positive Age by HbA1c interaction was revealed β = .39, p = .01; R^2 = 0.30, F (3, 43) = 5.76, p = .00 (Table 15). Interaction data are illustrated in Figure 9.

In summary, results revealed a significant inverse relationship between HbA1c and CERAD-WL. Age did not predict delayed recall. However, a

significant but positive interaction between HbA1c and Age on CERAD-WL was also observed, such that the younger individuals with lower levels of HbA1c recalled more words relative to those with higher levels of HbA1c. However, those with low HbA1c recalled fewer words with increasing age. Conversely, the participants with higher levels of HbA1c recalled more words with increasing age.

CERAD – Figure Recall. Race (β = -0.04, p = .78) and literacy (β = 0.24, p = 0.13) were not found to be significant predictors of performance and were not entered into the model as covariates. Hierarchical regression analyses were conducted to examine the impact of Age, HbA1c, and the Age by HbA1c interaction on free recall ability. Regression analysis revealed no effect of Age, β = -0.10, p = O.58; R^2 = 0.02, F (1, 41) = 1.03, p = .31. There was no effect of HbA1c, β = -0.15, p = 0.34; R^2 = O.04, F (2, 39) = 0.95, p = .39; and no Age by HbA1c interaction β = 0.20 p = .24; R^2 = 0.08, F(3, 41) = 1.10, p = .35 (see Table 16).

In summary, Age, HbA1c, and an Age by HbA1c interaction did not significantly predict the ability to recall geometric shapes on the CERAD Figure recall test.

Executive Functions

Verbal Fluency-category. Race, β = -.36 p = .02, was found to predict verbal fluency even after literacy was entered into the model literacy, β = -0.00, p = .96.

Hierarchical regression analyses were conducted to examine the impact of Age, HbA1c, and the Age by HbA1c interaction on the ability to generate exemplars of a semantic category while controlling for Race. Regression analysis revealed that while controlling for Race, Age was not a significant predictor of Verbal Fluency, β = 0.12, p = .45; R^2 = 0.12, F (2, 41) =2.75, p = .07. A significant effect of HbA1c was not shown, β = 0.14, p = .38; R^2 = 0.13, F (3, 41) =1.89, p = .14. However, a significant Age by HbA1c interaction was revealed, β = 0.34, p = 0.02; R^2 = 0.23, F (4, 41) =2.86, p = .03 (Figure 10). Race also remained a significant predictor of Verbal Fluency, β = 0.35, p = 0.03; R^2 = 0.12, F (1, 40) = 5.59, p = .02. Independent samples t-tests revealed that the Black participants generated significantly fewer words than the White participants, t(41) = 2.4, p = .01(see Table 17). Race effects are illustrated in Figure 11.

Race was shown to predict verbal fluency with the Black participants generating significantly fewer words than the White participants. Age and HbA1c were not found to be predictors; however, a significant interaction between Age and HbA1c was found. Participants with low levels of HbA1c generated fewer words than similarly-aged individuals with high HbA1c and demonstrated a slight decrease in performance with increasing age. The participants with higher levels of HbA1c generated more words than their similarly-aged cohorts and improved with increasing age.

Clock Drawing. A Mann-Whitney U test was conducted on the Clock drawing test due to its non-normal distribution. The median of 7 for the HbA1c

variable was utilized as a dividing point. A significant difference was revealed (U = 137.00, p = .03), such that those below the median point of 7 had a higher mean rank (25.27) than those above the cut-off (17.35). Data for Mann-Whitney U test are presented in Table 18. Mean and Median data are presented in Table 19.

In sum, with regards to the FCSRT, Age and HbA1c, were not shown to be significant predictors. However, a trend towards an inverse relationship between Age by HbA1c emerged. In regards to the CERAD-WL Age was not shown to be a significant predictor of performance. However, increasing levels of HbA1c were shown to significantly predict lower performance on the CERAD-WL. Race was also shown to be a significant predictor, with Black participants recalling significantly fewer words than White participants. For the CERAD-WL delayed recall, both Age and HbA1c were shown to be predictors of performance. Further, a trend towards an Age by HbA1c interaction was also demonstrated. Those with higher levels of Hba1c improved with increasing Age but then declined after age 80; however they performed better than their similarly aged counterparts with low HbA1c.

In terms of executive functioning, verbal fluency was moderated by race, such that the Black participants generated fewer words than the White participants. Verbal fluency was not moderated by Age or HbA1c. However, a significant positive Age by HbA1c interaction was demonstrated, such that the younger participants with low levels of HbA1c generated fewer words than the younger individuals with high HbA1c, with a slight decrease in performance with increasing age. Conversely, participants with higher levels of HbA1c generated

more words than their low HbA1c counterparts and improved with increasing age. On the Clock drawing test, those with an HbA1c level ≤ 7 were better at the clock drawing task than those with Ha1c levels ≥7.

Discussion

Experiment 1: overview

For experiment 1 we sought to examine whether or not individuals with DM perform worse than HCs and individuals with HD+HTN and HTN on tests of memory and executive functions. Specifically, our aim was to rule out the contribution of HTN and HD to performance on measures of cognition among individuals with DM. We expected to find that individuals with DM would perform worse than the HC and individuals with HTN and HD on cognitive tests.

FCSRT- Free Recall. Our hypothesis concerning impaired memory among participants with DM was confirmed to an extent. That is, we were able to demonstrate that individuals with DM were impaired relative to HC on the free recall portion of the FCSRT. However, we were not able to show that it was the effect of DM, per se, that was impairing performance. Rather, it appears that the poor performance associated with DM might have also been driven by HD as the data revealed that the HTN+HD group was also significantly impaired relative to the HCs. Further analyses of the data showed the HTN+HD and the DM groups were comparable to each other in their capacity for free recall on the FCSR.

Although we were not able to rule out the contribution of HD to DM performance, FCSRT results permitted us to rule out the presence of HTN as a possible confound. Specifically, we demonstrated that individuals with HTN were comparable to HCs in their ability to recall the 16 items presented in the FCSRT.

Thus, in the case of the free recall portion of the FCSR, we were unable to state that DM, per se, impairs free recall. Indeed, based on our results, it appears that HD might have played a role in the performance of the DM group.

CERAD-WL. The prediction for word list learning, as measured by the CERAD-WL, was not confirmed by our findings because there was no significant difference among the groups. A significant effect of VIQ, however, was revealed. Further analyses revealed that those who had a VIQ score of ≥ 111 recalled more words relative to those who scored ≤111.

CERAD-WL (delayed recall). Delayed recall for verbal information was assessed with the delayed recall portion of the CERAD-WL. The DM, HTN, and HTN+HD groups all recalled fewer words than the HC group; however, the difference did not reach significance. Since the delayed recall portion of the CERAD-WL is purported to be an effective measure to distinguish dementia from normal functioning, our results were not surprising given the absence of participants with a diagnosis of dementia in this present study. VIQ was shown to be associated with the capacity to recall a list of words following a delay. Once again, the data pointed to the fact that higher VIQ is associated with better word-list learning.

CERAD Figure Recall. Recall of non-verbal information was examined via the CERAD-Figure recall test. The DM and HTN+HD groups' ability to recall geometric shapes following a delay was worse than that of HCs.

In terms of memory, a discrepancy between performance on the CERAD-WL tests and the FCSR tests emerged. To recapitulate, the DM and HTN+HD groups recalled fewer items relative to the HC group on the FCSRT and the CERAD Figure Recall. Conversely, there was no difference among the groups on the CERAD-WL test.

There are a number of plausible explanations for the discrepant findings on the measures of memory. For example, inquiries concerning tests of memory for non-verbal information (i.e., CERAD Figure Recall) versus memory for verbal information (i.e., CERAD–WL) have shown inconsistencies in performance due to factors such as the difference in neural substrates employed for various memory tasks (see Wig et al., 2004). However, most relevant to the current results is the fact that the CERAD results were utilized as part of the diagnostic protocol for the larger Culture-Fair study (Grober, Hall, McGinn, Nicholls, & Stanford et al., 2008). Therefore, it is highly possible that individuals who met the other criteria for dementia and performed poorly on the CERAD-WL test were not included in the current study. Excluding participants who performed poorly on the CERAD test might have resulted in the range of the data being restricted, making it difficult to detect significant results.

In addition to the possibility that a restricted range of data influenced the outcome, another explanation is that the FCSRT is a controlled measure of memory, whereas the CERAD is not. As previously noted, the FCSRT controls for factors that impair memory performance, namely inattention and information processing. Conversely, the CERAD does not control for inattention and might actually be measuring attention rather than memory. Thus, the spared performance of the medical groups could be due to intact attentional abilities.

Clock Drawing and Verbal Fluency. The performance of all medical groups (i.e., DM, HTN, HDN+HD, & HC) was at ceiling on the clock drawing test. With regards to verbal fluency, although the DM group performed worse than the HTN, HTN+HD, and HC groups, the difference did not reach significance. Not

surprisingly, the capacity to generate exemplars of a semantic category was shown to be driven by VIQ, such that those with a VIQ of greater than or equal o 111 generated significantly more words than those with a VIQ below 111.

The Oldest-Old Hypothesis. We hypothesized that a marked difference between the oldest-old and young-old would be observed across all cognitive tests utilized in the current study. Indeed, the results confirmed our hypotheses: the oldest-old recalled significantly fewer words on the FCSRT, the CERAD-WL immediate and delayed, and the CERAD Figure recall test relative to the young-old. Verbal fluency and clock drawing capabilities were also influenced by age, such that the oldest-old performed worse than the young-old. The age by medical group interaction that was put forth in the study was not borne out. We hypothesized that an interaction between age and DM would emerge based on the accelerated brain aging hypothesis (Awad et al., 2004). However, the data did not bear out our prediction. We failed to demonstrate an interaction between age and DM or age and HTN or HD on any of the tests.

Summary of Experiment 1 Results

In sum, based on the current study results, DM was shown to be associated with poor performance on the FCSRT. However, the data suggest that while HTN, per se, might not have played a role in the DM Group's performance on the FCSRT, HD was a likely contributor. This effect for medical illness was not observed on the CERAD word list learning test perhaps due to procedural differences or statistical constraints. Memory for non-verbal information (CERAD-Figure Recall) and executive functions were not influenced by medical illness.

The contribution of HD to cognition. The current finding pointing to HD as a possible contributor to poor performance on the FCSRT and the CERAD Figure recall among those with DM is not surprising. HD has been consistently shown in the medical literature as being strongly linked to DM (Awad et al., 2004). Importantly, HD has been shown to be associated with impaired cognitive functioning in and of itself (Cosway et al., 2001). However, inquiries concerning HD and cognitive impairment are equivocal due to the complex nature of HD. Methodological difference is one source of the inconsistency. Like the current study, researchers have opted to group all subtypes of cardiac issues into an umbrella category of HD. A number of investigators have examined specific cardiac disturbances (e.g., myocardial infarction [MI] and atrial fibrillation [AFIB]) and within these specific subtypes, the evidence is equivocal. For instance, some authors suggest that there is no link between MI and impaired cognition (Bursi et al., 2006). Grubb, Simpson, and Fox (2000) demonstrated that patients with MI (at least 1 year before assessment) and those with moderate-to-severe cardiac failure do not have significantly impaired memory. Others have revealed that following MI, patients had a higher risk of cognitive impairment or dementia due to brain hypoperfusion (Zuccala et al. 2001) and reduced cardiac input (Bursi et al., 2006). The Bronx Aging study, a prospective cohort study, found a fivefold increase in the risk of developing dementia among women with a history of MI (Aronson et al., 1990).

Investigations examining AFIB (i.e., atypical heart beat), and cognition have also produced outcomes that have found no association with cognitive

impairment after a 3 year follow-up (e.g., Park et al., 2007). On the other hand, Kilander et al. (1998) found that independent of stroke, diabetes, and HTN, AFIB was a determinant of low cognitive functioning.

The contribution of HTN to cognition. The current finding demonstrating intact cognitive functioning among those with HTN stands in contrast to other findings that have shown HTN to be significantly impaired relative to healthy controls on a number of measures of cognition. For instance, several studies have shown an inverse relationship between blood pressure and verbal fluency (e.g., Elias et al., 1993; Skoog et al., 1996). Moreover, Brady, Spiro, and Gaziano (2005) found that hypertensives had a diminished ability for verbal fluency and that the impairment was greatest among older participants.

There is a wealth of literature showing that HTN is strongly associated with mild or sub-clinical to marked impairment on measures of memory. Several authors suggested a linear inverse relationship between HTN and memory (i.e., higher blood pressure is associated with lower cognitive function (Brady et al., 2005; Harrington et al., 2000). Interestingly, Waldstein et al. (2005) reported impaired executive functioning and memory performance among those with low blood pressure. Thus, it can be argued that blood pressure and cognition have a U-shaped relationship. Additionally, education can mediate performance, which results in a J-shaped between blood pressure and cognition, such that among non-medicated persons, those with higher BP display poorer performance than individuals with mid-range BP; individuals with lower BP also display poorer performance than those with mid-range BP (Waldstein et al., 2005). Regardless

of the trajectory of the relationship, the point most relevant to the current study is that if blood pressure is too high, then cognition can be impaired.

A possible explanation for our findings of a relatively cognitively intact HTN group, particularly on the FCSRT and CERAD Figure Recall, is that the hypertensives in the current study were being treated with antihypertensive medication (e.g., diuretics, angiotensin II receptor blocker, and beta blockers) at the time of testing. It is well-established that patients with treated HTN experience fewer cardiovascular disease events (Nash & Fillet, 2006) and have a reduced risk of cardiovascular mortality (Veld et al., 2001). Based on the current results, it is conceivable that hypertensive medication may also exert a neuroprotective indication. One consequence would be a reduced risk of developing dementia or mild cognitive impairment, which would be demonstrated by spared capacity on tests of cognition among treated HTNs. Unfortunately, few epidemiological studies have directly investigated this line of thinking (Veld et al., 2001). Typically, hypertensives studied in research have been diagnosed but untreated (Brady et al., 2005; Forette et al., 1998).

VIQ and cognition: A case for cognitive reserve. The current results provide support for the idea of cognitive reserve in patients with medical illness. Cognitive reserve has been discussed widely in the Alzheimer's disease (AD) literature to explain the findings of advanced brain pathology with no behavioral evidence. Stern (2000) posits that the better-educated or individuals with higher levels of intelligence have a greater cognitive reserve and tend not to readily show the effects of brain pathology. In the current inquiry, we found that individuals with higher VIQ performed better than individuals with lower VIQ on

the CERAD-WL, CERAD Figure recall, Verbal Fluency, and Clock Drawing tests, consistent with the cognitive reserve hypothesis. Nonetheless, like the lower VIQ individuals, those with higher VIQ were diagnosed with diseases that have been implicated in poor cognitive performance (i.e., HTN, HD, & DM). Thus, it appears that in or study, intelligence had a protective effect against medical illnesses associated with cognitive impairment. However, thorough investigations examining interactions among VIQ, disease, and cognition would be beneficial to further elucidate a possible relationship between cognitive reserve and medical illness.

Age and cognition. Our results illustrating a marked decrease in cognitive function with increasing age were not surprising. The cognitive and neuropsychological literatures are replete with similar evidence. However, there is a degree of variability in terms of the age at which deterioration occurs. As previously described, a gradual decline in immediate recall has been shown to occur at age 50 with more rapid degeneration occurring after age 80. Others have found gradual decrements in memory commencing as young as age 30 (see Haaland, et al., 2003). Thus, our results are consistent with the literature showing a decline in memory and executive functions among older persons.

Experiment 2 Overview

For experiment 2 our goal was to determine whether or not there is a relationship between HbA1c and cognitive functions. We expected to find an inverse relationship between HbA1c and measures of memory and executive functions.

Effect of HbA1c on cognition. We examined the extent to which increasing HbA1c levels impairs cognition. We hypothesized that with increasing HbA1c, there would be a notable decrease in scores on tests of memory and executive functioning.

As previously noted, a number of studies have described the detrimental effect of elevated hemoglobin on the PNS. However, few studies have examined the effects of uncontrolled diabetes on the CNS and cognition. Based on previously discussed research showing the detrimental physical effects of elevated glucose on the brain, namely, within temporal and frontal regions, we hypothesized that there would be a notable decline in memory and executive functioning with increasing HbA1c levels.

Further examination of the cognitive abilities among diabetics in the present study may seem counterintuitive given the current results pointing to a relative sparing of functioning across a number of tests. The rationale for conducting subsequent data analyses on this group rests on the possibility that within the DM group, there may be a larger range, such that some of the individuals might have negligible to minimal deficits whereas others might be markedly impaired.

Results of the current study confirmed a relationship between HbA1c and performance on some cognitive tests. More specifically, the data illustrated an inverse relationship between HbA1c and scores on the CERAD-WL and CERAD-WL delayed recall, such that with increasing levels of HbA1c, the capacity to recall a list of words diminished, both immediately and following a delay.

When HbA1c was divided at a median point of 7, in order to evaluate the Clock drawing test, the results also confirmed the idea that elevated HbA1c is associated with poorer cognition. We found that individuals with HbA1c below the current study median (i.e. 7) were better at clock drawing than those above the median point. Interestingly, the median HbA1c utilized in the current study is also the dividing point established in the medical literature to distinguish compliant versus non compliant diabetics. To reiterate, an HbA1c level of over 7 suggests that an individual with DM does not adhere to one or all components of his or her treatment regimen (e.g., medication use, diet, and exercise).

Effect of age and HbA1c on cognition. Age was not associated with performance on any of the memory tests in the current study among the DM group. An Age by Hemoglobin interaction emerged but the interaction was in contrast to what was hypothesized. The current study predicted that with higher levels of HbA1c, the effects of increasing age would be more deleterious than that of comparably aged individuals with lower levels of HbA1c. Results of the study, however, demonstrated that among individuals with HbA1c 1 *SD* below the mean or lower, those who were at the younger end of the age range (e.g., <70) recalled more words than those of comparable Age with HbA1c 1 *SD* above the mean on both the CERAD-WL and CERAD-WL delayed. This finding, to an extent, revealed that at least among the younger of the young-old, higher levels of HbA1c were related to poorer recall ability. However, the trajectory of the performance was not expected for the individuals with higher levels of HbA1c. While the performance of individuals with lower HbA1c levels

deteriorated with increasing age, it appears that the recall capabilities of those with higher HbA1c levels improved with age.

In terms of verbal fluency, results revealed that among the younger of the young-old, those with higher levels of Hba1c generated more words than the similar-aged individuals with low levels of HbA1c. Those with lower HbA1c generated slightly fewer words with increasing age. On the other hand, among those with higher levels of HbA1c, performance appeared to improve with increasing age.

Thus, among individuals with low HbA1c, the expected age effect was observed on both the CERAD -WL tests. However, among participants with high HbA1c leves, the pattern was such that increasing age was associated with better performance. A similar pattern was observed with the verbal fluency data.

Explanation of the age by HbA1c interaction. The results showing that performance improved with increasing Age among those with elevated HbA1c levels suggest that there might be a protective effect of elevated blood sugar/glucose among older persons. Indeed, it has been effectively shown that by experimentally increasing glucose levels, memory performance among individuals with poor memory and/or poor glucose regulation was enhanced. This effect was most notable among older persons and individuals with AD relative to young, healthy participants (see Kaplan, Greenwood, Winocour, & Wolever, 2008). Although the Kaplan et al. (2008) findings offer an explanation for the current results, it is important to note the Kaplan et al. study was carried out in an experimental setting and did not include diabetic individuals. As

previously discussed, chronically high levels of HbA1c have been shown to cause physical abnormalities in the human brain.

Another explanation for the age by HbA1c interaction is the possibility that older individuals with high levels of HbAa1c might simply be physically stronger than their counterparts with lower levels of HbA1c. However, a decrease in performance due to age should still have been observed, although not as steep.

Finally, it is possible that if the study design had been longitudinal rather than cross-sectional, a decrease in performance among the older individuals with elevated HbA1c might have been borne out. Specifically, with a longitudinal design we would have been able to evaluate changes over time, via a repeated-measures design. Perhaps with a longitudinal, repeated measures design an age-related decline among those with elevated HbA1c might have emerged.

Effect of race on cognition. Race predicted performance on the CERAD-WL and the verbal fluency tests, even after adjustments for literacy, a mediator of the race effect (Manly et al. 2005). The Black participants with DM recalled more words on the CERAD-WL and generated fewer words on the verbal fluency test. It remains unclear what drives the race effect in the present study as race appears to be a correlate of many other factors that affect cognition.

Summary of Overall Results

The current study had several interesting findings. First, the notion that cognitive impairment among diabetics is a direct consequence of the effects of DM itself needs to be re-examined. Based on the present results, it appears that the memory impairment associated with DM may be due, in part, to the medical illnesses that are comorbid with DM, namely HD.

The present findings bode well for antihypertensive therapy, which is the standard of care for HTN participants in the present study. Specifically, the data suggest a possible neuroprotective indication for antihypertensive therapy in that the individuals with HTN were comparable to HCs on all of tests employed in the current study. Most notably, the individuals with HTN were comparable to HC on the FCSRT and the CERAD Figure recall while the DM and HTN+HD groups performed worse than the HCs.

In addition to suggesting a neuroprotective indication for antihypertensive therapy, our data also suggest a neuroprotective indication for therapy aimed at controlling blood sugar levels among diabetics. Our results indicate that elevated levels of HbA1c are associated with impaired cognitive ability. Specifically, in the second experiment, our hypothesis of an inverse relationship between HbA1c and recall on measures of memory was substantiated.

Interestingly, an inconsistency in performance among individuals with elevated levels of HbA1c on measures of memory emerged. That is, an inverse relationship between HbA1c and recall on the CERAD-WL tests was shown but there was no relationship between HbA1c and free recall on the FCSRT.

As previously discussed, the CERAD-WL was utilized as part of the diagnostic procedure for the larger study, whereas the FCSRT was not. As a consequence, it is possible that only the participants who performed well on the CERAD were included in the current investigation. However, since recall was lower on the CERAD and not on the FCSRT among individuals with elevated HbA1C, the possibility of biased or truncated CERAD data does not seem to be an issue.

The discrepant results on the CERAD-WL versus the FCSRT point to the possibility that HbA1c might be linked to poor attention rather than to poor memory. In order to support this assertion, it is necessary to understand the procedural differences between the CERAD and the FCSRT. As previously discussed, one of the benefits of the FCSRT is that memory is facilitated because the study phase of the FCSRT controls for factors that could impair learning and recall, namely poor attention. Attention is controlled for and deeper semantic procssing of the to-be-remembered items is facilitated by the provision of cues at the time of encoding with the FCSRT (Grober et al., 2000). Thus, by controlling for attentional difficulties, it is possible that the FCSRT provides a purer measure of memory than the CERAD-WL. In contrast to the FCSRT, on the CERAD test, participants read aloud the 10 to-be-remembered words then recalled the list of words over 3 trials. Attention is not controlled and deeper semantic encoding is not facilitated.

Controlling for attention is particularly important among older persons because age-related decrements in attention are well-established in the literature (Choa & Knight, 1997). Craik (1977) posits that divided attention is greatly affected by increasing age. This notion has been borne out in several studies (for review, see Choa & Knight, 1997). Moreover, both selective and sustained attention have been described as being vulnerable to the effects of aging (McDowd & Shaw, 2000). Thus, it is clear that various types of attention are negatively affected by increasing age.

Research has consistently shown that attention and memory are strongly intertwined as one needs intact attentional abilities in order to perform well on

memory tests (Craik, Govoni, Naveah-Benjamin, & Anderson, 1996). Thus, a test of memory that controls attention is highly beneficial, especially when conducting research with older persons. Based on the well-established literature concerning the link between attention and memory among older persons, we suggest that the poor recall observed on the CERAD among individuals with elevated levels of HbA1c might be due to inattention. Conversely, the lack of a relationship between HbA1c and the FCSRT implies that elevated HbA1 might not impair memory. This needs to be tested in future work that directly examines the relationship between attention and HbA1c.

Limitations of the current study

Some limitations to the current study warrant considerations. Although this inquiry utilized information from thorough medical chart review, a few problematic issues were unavoidable. We were unable to ascertain when the patients in both the HTN+HD group and DM groups were initially diagnosed with their condition. Duration information is important because the period of time between the initial MI incident, for example, and cognitive testing affects the relationship observed between MI and cognition (see Petrovitch et al., 1998). Unfortunately, we were unable to consider duration of HD in our analysis. Similarly, we were unable to obtain information about the duration of the diabetes. Importantly, it has been shown that DM can be asymptomatic in its early stages and consequently, many individuals have had the disease for several years before receiving initial diagnosis and treatment (Gregg et al., 2004). Thus, based on the relative silence of diabetes symptoms, duration or onset data for HbA1c might not always be accurate. Data on the duration of the

diabetes would have benefited the current study in that some have shown the duration of DM to be important with regards to performance on tests of cognition, with longer duration associated with poorer cognition (Cosway et al., 2001).

As previously noted, those with HTN were being treated with various forms of antihypertensive medication at the time of testing. However, there was no information on whether or not the treated HTNs were compliant with their medication use and whether or not their blood pressure was within the normal range at the time of testing. Although the hypertensives in this study performed as well as healthy controls on a test of memory, HTN compliance data would have been valuable information to have had. Indeed, as previously discussed, HTN has been shown to impair cognition. However, Paran, Anson, and Reuvi (2003) have reported that moderately elevated blood pressure actually enhances cognition among individuals over the age of 70.

In addition to incomplete medical information, another limitation in the current study relates to interpreting the statistical data of the CERAD. As previously noted, the CERAD tests were employed in the determination of dementia status and as a result, the sample might have included individuals who performed well on the CERAD. Including only individuals that performed well on the CERAD tests might have resulted in a restricted a data range, making it difficult to detect a significant effect.

Finally, there was a degree of selection bias in this study. All of the participants were out-patients at the Geriatrics Ambulatory Practice of Montefiore Medical Center. Thus, all of the participants had access to medical care and

fairly regular medical visits (usually every three or four months) and might not necessarily be representative of the general population.

Clinical Implications

Despite some of the limitations noted, there are important clinical implications of this study. The most noteworthy implication is the importance of compliance and management of hypertension and diabetes on cognition, be it through dietary means, medical intervention, or both. Another implication is our study provides valuable information to the clinical practice of neuropsychologist and physicians. Specifically, our results reveal that medial illnesses such as DM and HD are associated with compromised memory and executive functions. Further, we demonstrated that elevated HbA1c levels are associated with impaired memory and executive functions. Thus, knowledge of a patients' medical diagnostic status (DM or HD) and of a diabetics HbA1c level could inform neuropsychologists and physicians about possible cognitive impairment.

Future Directions

Because we did not find an effect of medical group in Experiment 1, we plan to further investigate our results and examine whether or not comorbidity of disease played a role in the outcome. The Charlson comorbidity index developed by Charlson, Pompei, and McKenzie (1987) will be employed to evaluate comorbidity. The Charlson Index assigns weights to diseases, such as hypertension and heart disease, and provides a measure of medical burden.

The results of Experiment 2 showed an inverse relationship between HbA1c and memory (word-list learning) based on performance on the CERAD. Future studies could focus on examining a broader range of cognitive deficits among individuals with DM. This could be achieved with comprehensive test batteries that examine various types of memory (e.g., memory for contextual verbal information), a range of executive functions (e.g., planning and set-shifting), and processing speed.

Further, based on our data showing that an elevated level of HbA1c is associated with impaired memory and possibly attention, studies relating cognitive functioning to daily living and compliance with a treatment regimen would also be of tremendous benefit.

Experiment 2 revealed an interaction effect that was unexpected, such that among the individuals with high HbA1c there was an increase in recall with increasing age. In order to elucidate this finding, we plan to examine factors that might have moderated these results, such as age, race, and depressive symptoms among the individuals with high HbA1c.

Table 1

Medical Group Demographic Variables.

	Medical Groups			
Variable	DM	HTN	HTN+HD	HC
Sex				
Male				
n	10 (22 %)	7 (10%)	11 (14%)	5 (14%)
Female				
n	46 (78%)	61 (90%)	42 (86%)	30 (86%)
Race *				
Black				
n	30 (65%)	29 (43%)	27 (51%)	12 (34%)
White				
n	16 (34%)	39 (57%)	26 (49%)	23 (66%)
Handedness				
Left				
n	4 (9 %)	4 (6%)	3 (6%)	3 (9%)
Right				
n	40 (87%)	61 (91%)	48 (91%)	32 (91%)
Ambidextrous				
n	2 (4%)	2 (3%)	2 (3%)	0
Age				
M	76.91	77.68	78.58	77.25
SD	7.23	7.14	5.96	7.53
Years of education				
M	12.35	12.99	12.83	12.89
SD	2.82	3.41	3.45	2.93

Note. There are significantly more Blacks in the DM group and significantly more Whites in the HC group, χ^2 (3, N =202) =6.2, p = .04.
Medical groups; DM= Type 2 dm, HTN = hypertension,
HTN+ HD = hypertension & heart disease, HC = healthy controls.

Table 2

Medical Group Screening Test and Neuropsychological Tests.

	Medical Groups			
Screening Measure	DM	HTN	HTN+HD	HC
	n = 46	*n* = 68	*n* = 53	*n* = 35
MMSE				
M	26.95	27.68	26.94	27.77
SD	2.83	2.40	2.75	2.11
GDS				
M	3.02	2.49	2.64	2.63
SD	2.67	2.71	2.18	1.88
Verbal IQ				
M	104.52	110.13	111.37	112.99
SD	12.79	13.70	12.32	11.17
Naming				
Mean rank	101.62	100.60	98.83	101.83
Mdn	16.00	16.00	16.00	16.00

Note. The DM group had significantly lower verbal IQ than the HC and the HTN+HD group, $F(2,201) = 2.9$, $p = 0.00$

Table 3

Analysis of Variance for FCSRT.

Source	df	F
Group	3	4.90**
Age	29	2.01 **
Error	168	
DM x Age	15	0.65
HTN X Age	17	0.84
HTN+HD x Age	19	0.33

Note. F values indicated with an asterisk represents significant effects (* p< .05, * * p < .01).

Table 4

Medical Group Test Means and Standard Deviations

	Medical Groups			
Test	DM	HTN	HTN+HD	HC
FCSRT	*n* = 46	*n* = 67	*n* = 53	*n* = 35
M	28.02 **	29.70	26.00 **	30.54
SD	7.90	6.39	7.73	6.98
r	0.13	0.12	0.25	
CERAD – WL	*n* = 45	*n* = 64	*n* = 63	*n* = 35
M	18.37	18.71	18.41	20.00
SD	4.18	4.06	4.81	3.73
CERAD – WL Delayed recall	*n* = 45	*n* = 64	*n* = 53	*n* = 35
M	5.47	5.75	5.34	6.11
SD	2.33	2.16	2.48	2.04
CERAD: Figure – recall	*n* = 42	*n* = 64	*n* = 52	*n* = 35
Mean rank	87.29	102.45	86.0	115.03
Mdn	6.0	7.0	6.5	7.0
Clock Drawing	*n* = 42	*n* = 67	*n* = 53	*n* = 35
Mean rank	96.48	104.02	97.69	96.91
Mdn	40.00	40.00	39.00	40.00

Note. Medical group; DM = diabetes mellitus, HTN = hypertension, HTN+HD = hypertension + heart disease.
Note. On the FCSRT, planned comparisons reveal that the DM and the HTN+HD performed worse than controls. The HTN+HD performed worse than the HTN group.
Note. The mean ranks presented for the CERAD- test and Clock Drawing are the overall test ranks.
Effect sizes are reported for significant results.

* p< .05, * * p < .01

Table 5

Summary of *t* -test results for Age Group performance

	Age Groups	
Test	Young- old	Oldest- old
FCSRT		
M	30.09**	25.91**
SD	6.52	7.94
r	0.31	
CERAD – WL		
M	19.91 **	16 .90**
SD	4.03	3.96
r	0.44	
CERAD – WL Delayed recall		
M	6.16 *	4.77*
SD	2.01	2.41
r	0.30	
CERAD: Figure (recall)		
Mdn	7.00 **	5.00 **
Mean rank	109.73	75.13
r	*-0.34*	
Clock Drawing		
Mdn	40.00 **	39 .00**
Mean rank	109.14	82.15
r	-0.23	
Verbal Fluency Category		
M	38.42	34.17
SD	10.56	9.24

Note. Significant differences between age groups are indicated by an asterisk (* $p < .05$, ** $p < .01$).
Young- old = 65-80 yrs.; oldest- old = 81 +

Table 6

Analysis of Variance for CERAD- WL.

Source	df	F
Group	3	2.08
Age	28	2.94 **
IQ	1	7.76 **
Error	164	
DM x Age	15	0.79
HTN x Age	17	0.98
HTN+HD x Age	16	0.93

Note. F values indicated with an asterisk represent significant effects (* p< .05, * * p < .01).

Table 7

Analysis of Variance for CERAD- WL delayed recall.

Source	df	F
Group	3	0.88
Age	28	2.26 **
IQ	1	15.35**
Error	164	
DM x Age	15	0.85
HTN x Age	17	0.74
HTN+HD x Age	16	0.38

Note. F values indicated with an asterisk represent significant effects (* p< .05, * * p < .01).

Table 8

Kruskal Wallis on CERAD Figure recall Test.

	df	χ^2
CERAD- Figure recall test	3	7.65 *

Note: Kruskal- Wallis Test revealed a significant effect of Group.
p = .05

Table 9

Mann- Whitney on Age Group performance on CERAD- Figure Recall Test.

	U
CERAD- Figure Recall Test	2778.00**

Note. Mann-Whitney U values indicated with an asterisk represent significant effects (* p< .05, * * p < .01)
Age- Group: young-old = 65-80 yrs.; oldest- old = 81 +

Table 10

Analysis of Variance for Verbal Fluency-category.

Source	df	F
Group	3	0.59
Age	28	1.49
IQ	1	62.9 **
Race	1	0.20
DM x Age	15	1.66
HTN X Age	17	1.15
HTN+HD x Age	16	0.64

Note. F values indicated with an asterisk represent significant effects (* p< .05, * * p < .01).

Table 11

Kruskal Wallis on Clock Drawing

	df	χ^2
Clock Drawing Test	3	0.81

Note. There was no significant effect of Group, $p = .87$

Table 12

Mann- Whitney on Age Group performance on Clock Drawing

	U
CERAD-Figure recall (recall)	3304.00**

Note. Mann-Whitney U values indicated with an asterisk represent significant effects * p< .05, * * p < .01
Age-Group: young-old = 65-80 yrs.; oldest- old = 81 +

Table 13

Summary of Multiple Regression Analysis for predicting the effect of HbA1c on FCSRT performance (*N*= 44).

Variable	*B*	*SE B*	β
Model 1			
Constant	28.77	1.10	
Age	-0.20	0.16	-0.19
Model 2			
Constant	28.90	1.08	
Age	-0.24	0.16	-0.23
HbA1c	-1.47	0.83	-0.26
Model 3			
Constant	29.20	1.05	
Age	-0.10	0.17	-0.10
HbA1c	-1.49	0.81	-0.27
HbA1c x age	0.28	0.15	0.31

Note. R^2 =0.04 for Model 1; Model 2: ΔR^2 = 0.06 (p =.10). Model 3: ΔR^2 = 0.08 (p =0.04)*
Covariates Race and Age were not used in this model. Age was entered into the model first as it has been shown in the current study to significantly impair performance on tests of cognition.

Table 14

Summary of Multiple Regression Analysis for predicting the effect of HbA1c on CERAD - WL performance (*N*= 44)

Variable	*B*	*SE B*	β
Model 1			
Constant	16.88	0.95	
Race	2.70	1.19	0.33*
Model 2			
Constant	17.14	1.00	
Race	2.32	1.27	0.28
Age	-0.08	0.09	-0.13
Model 3			
Constant	16.97	0.94	
Race	2.76	1.20	0.38*
Age	-0.20	0.09	-0.17
HbA1c	-1.13	0.42	-0.38*
Model 3			
Constant	17.08	0.90	
Race	2.85	1.14	0.35*
Age	-0.01	0.09	-0.02
HbA1c	-1.15	0.30	-0.38**
HbA1c x Age	0.16	0.07	0.33*

Note. R^2 = 0.11 for Model 1; Model 2: ΔR^2 = 0 .02 (p = 0.06). Model 3: ΔR^2 = .14(p = .00) Model 4: ΔR^2 = 0.09 (p = .00).
Values indicated with an asterisk represent significant effects (* p< .05, * * p < .01). Race was included in the model because it was found to be a significant covariate.

Table 15

Summary of Multiple Regression Analysis for predicting the effect of HbA1c on CERAD - WL delayed recall (*N*= 44)

Variable	*B*	*SE B*	β
Model 1			
Constant	6.28	0.37	
Age	-0.02	0.05	-0.06
Model 2			
Constant	5.66	0.31	
Age	-0.04	0.05	-0.13
HbA1c	0.70	0.24	-0.42 **
Model 3			
Constant	5.79	0.29	
Age	0.01	0.05	0.05
HbA1c	-0.71	0.22	-0.43 **
HbA1c x age	0.11	0.04	0.39 *

Note. R^2 = 0.00 for Model 1; Model 2: ΔR^2 = 0.17 (p = .01). Model 3: ΔR^2 = .12 (p = .02) Values indicated with an asterisk represent significant effects (* p< 0.05, * * p < .01). Covariates Race and Age were not used in this model.

Table 16

Summary of Multiple Regression Analysis for predicting the effect of HbA1c on CERAD – Figure test (*N*= 42)

Variable	*B*	*SE B*	β
Model 1			
Constant	6.09	0.50	
Age	-0.08	0.07	-0.16
Model 2			
Constant	6.13	0.51	
Age	-0.08	0.08	-0.18
HbA1c	-0.36	0.38	-0.15
Model 3			
Constant	6.22	0.51	
Age	-0.05	0.08	-0.10
HbA1c	-0.37	0.38	-0.15
HbA1c x age	0.08	0.07	0.20

Note. There were no significant findings in the FCSRT model
R^2 = 0.03 for Model 1; Model 2: ΔR^2 = 0.02 (p =.39). Model 3: ΔR^2 = 0.03 (p = .35)
Covariates Race and Age were not used in this model.

Table 17

Summary of Multiple Regression Analysis for predicting the effect of HbA1c on Verbal Fluency-category (n = 43)

Variable	*B*	*SE B*	β
Model 1			
Constant	45.85	4.5	
Race	-6.35	2.68	-0.35 *
Model 2			
Constant	45.49	4.84	
Race	-6.15	2.85.	-0.34 *
Age	0.02	0.09	0.04
Model 3			
Constant	44.80	5.07	
Race	-5.72	2.99	-0.32
Age	0.04	0.09	0.07
HbA1c	-0.57	1.09	-0.09
Model 3			
Constant	46.00	4.84	
Race	-6.26	2.8	-0.35 *
Age	0.07	0.09	0.12
HbA1c	-0.93	1.05	-0.14
HbA1c x Age	0.38	0.17	0.34 *

Note. R^2 = 0.12 for Model 1; Model 2: ΔR^2 = .00 (p = 0.07). Model 3: ΔR^2 = 0.01 (p =.14) Model 4: ΔR^2 = 0.11 (p = .03).
Values indicated with an asterisk represent significant effects (* p< .05, * * p < .01). Race was included in the model because it was found to be a significant covariate.

Table 18

Mann- Whitney HbA1c on Clock Drawing

	U
Clock Drawing	137.00 *

Note: Mann-Whitney U values indicated with an asterisk represent significant effects (* $p < .05$)

Table 19

Median and Mean Rank for HbA1c on Clock Drawing

	≤ 7	> 7
Mean Rank	25.27	17.35
Mdn	40.00	39.00

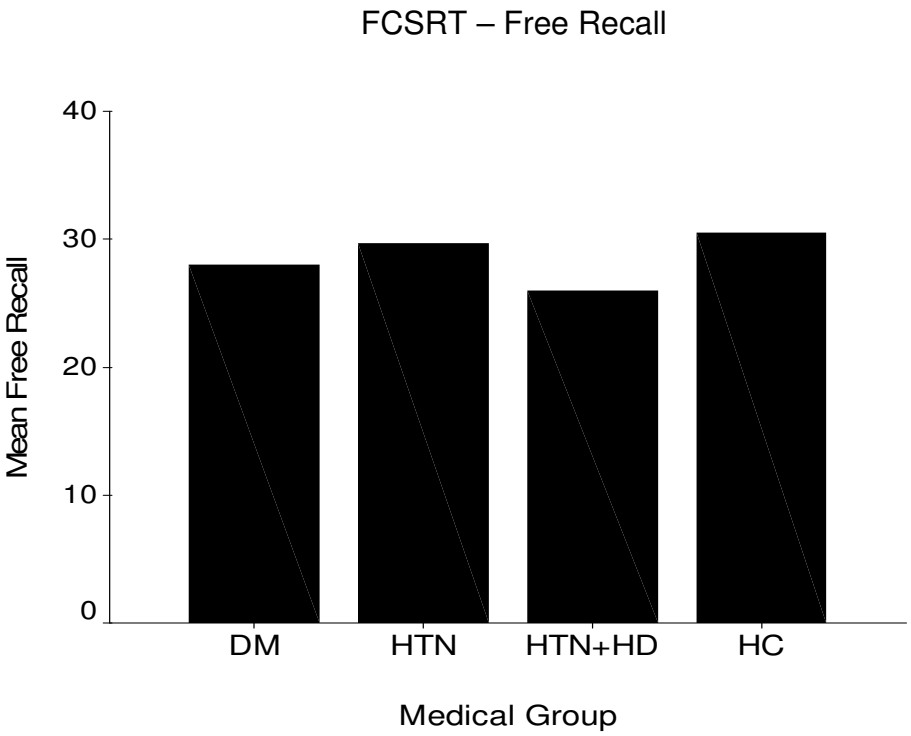

Figure 1. Medical Group means for FCSRT -Free Recall. The diabetic group (DM) and the hypertension & heart disease group (HTN+HD) performed significantly worse than healthy controls (HC) The probability levels were $p = .01$, and $p = .00$, respectively.

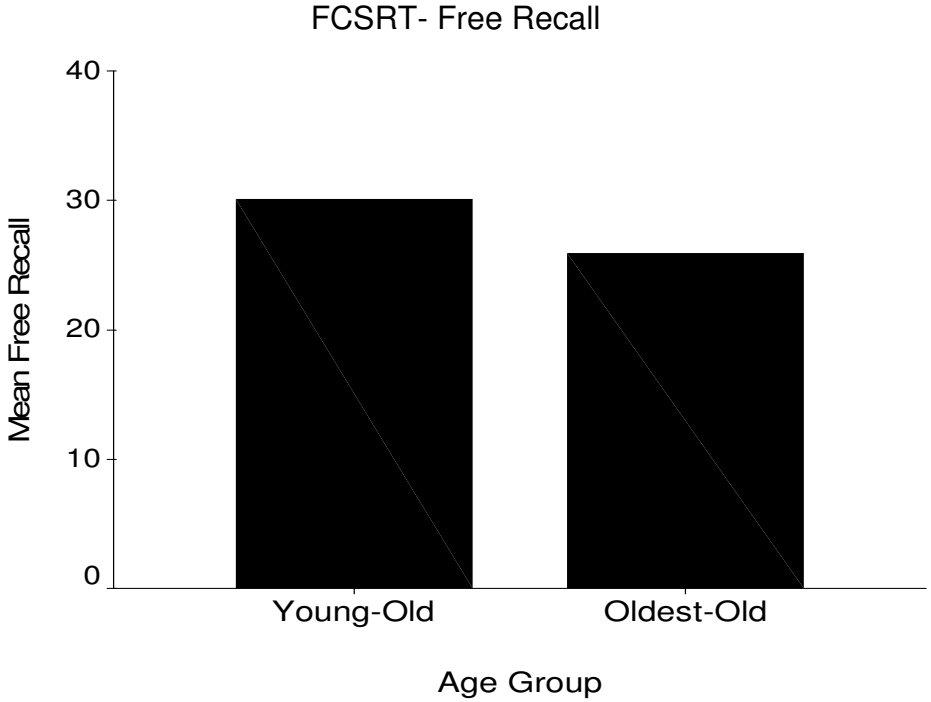

Figure 2. Age Group means for FCSRT Free Recall. The Oldest-Old recalled significantly fewer words than the Young-Old, $p = .00$

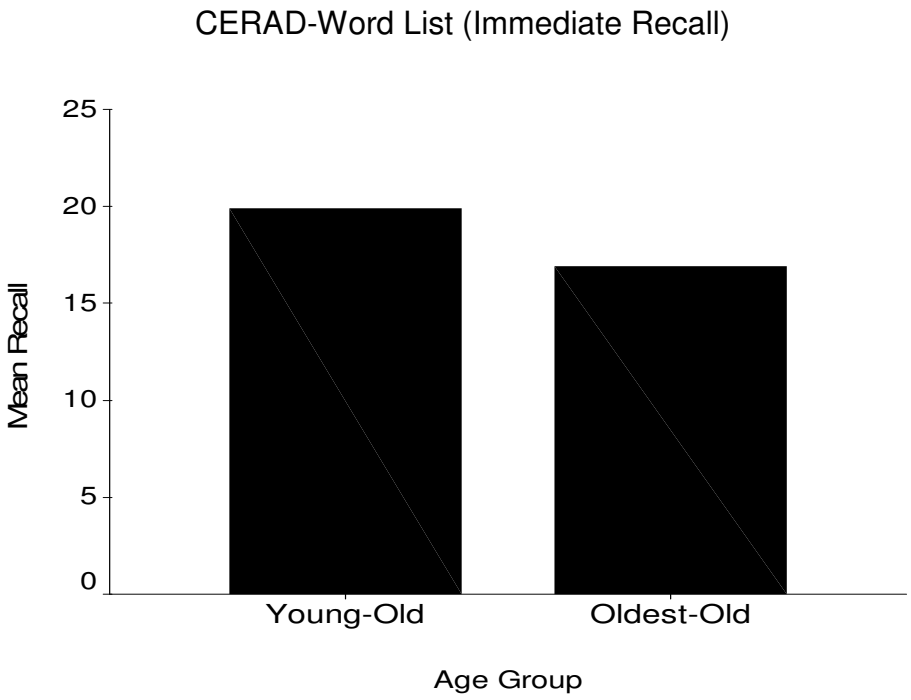

Figure 3 Age Group means for CERAD–WL. The Oldest-Old group recalled significantly fewer words than the Young-Old group, $p = .00$.

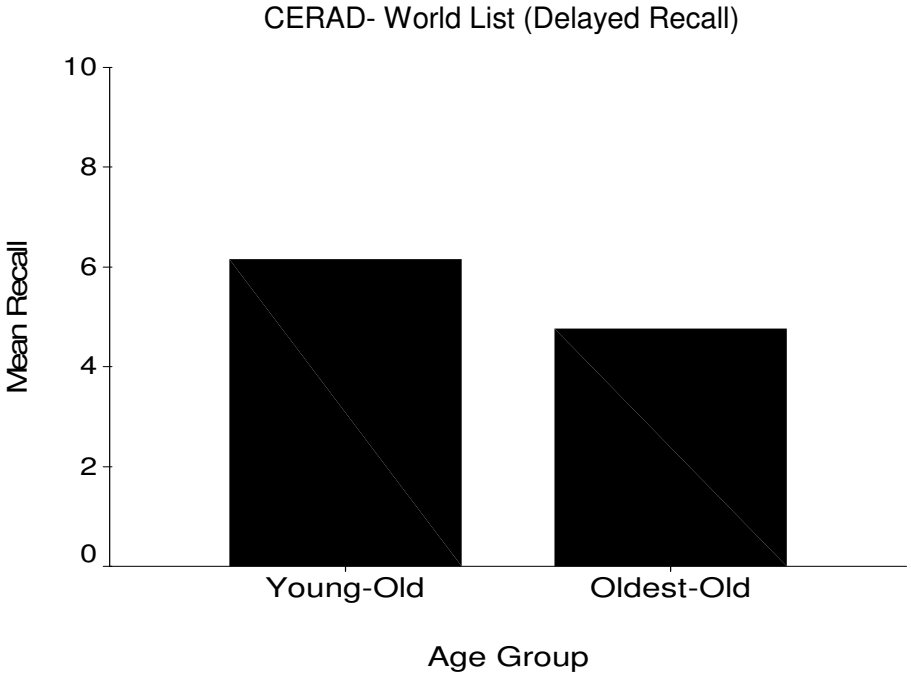

Figure 4. Age Group means for CERAD –WL delayed recall. The Oldest-Old group recalled significantly fewer words than the Young-Old group, $p = .00$.

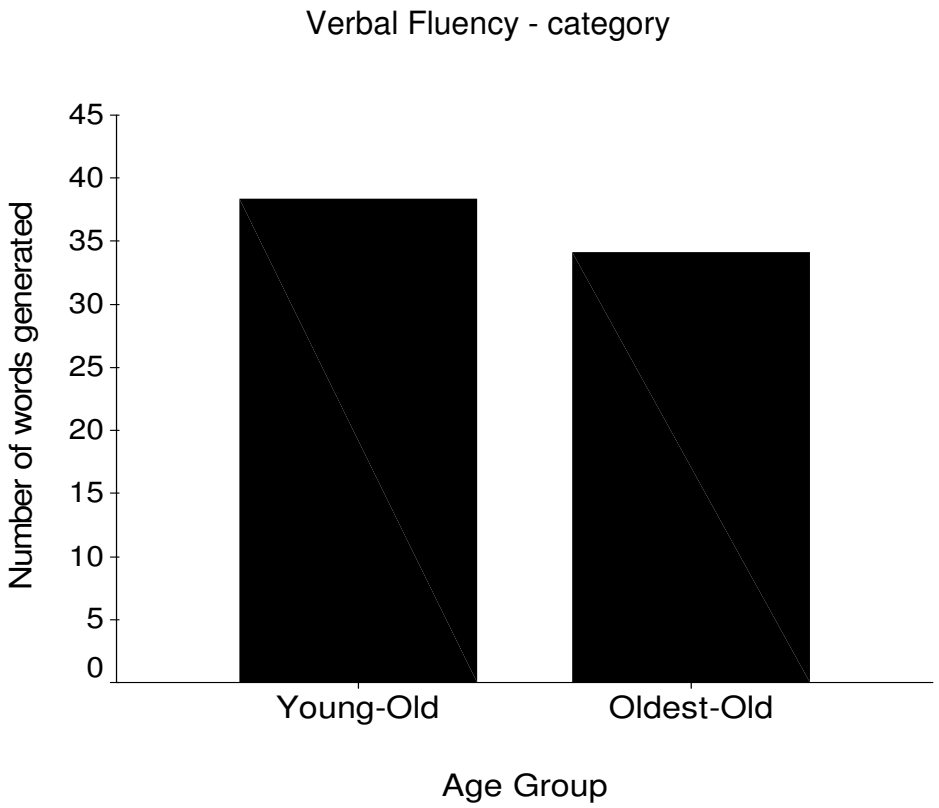

Figure 5. Age Group means for Verbal Fluency-category. The Oldest-Old group recalled significantly fewer words than the Young-Old group, p = .00.

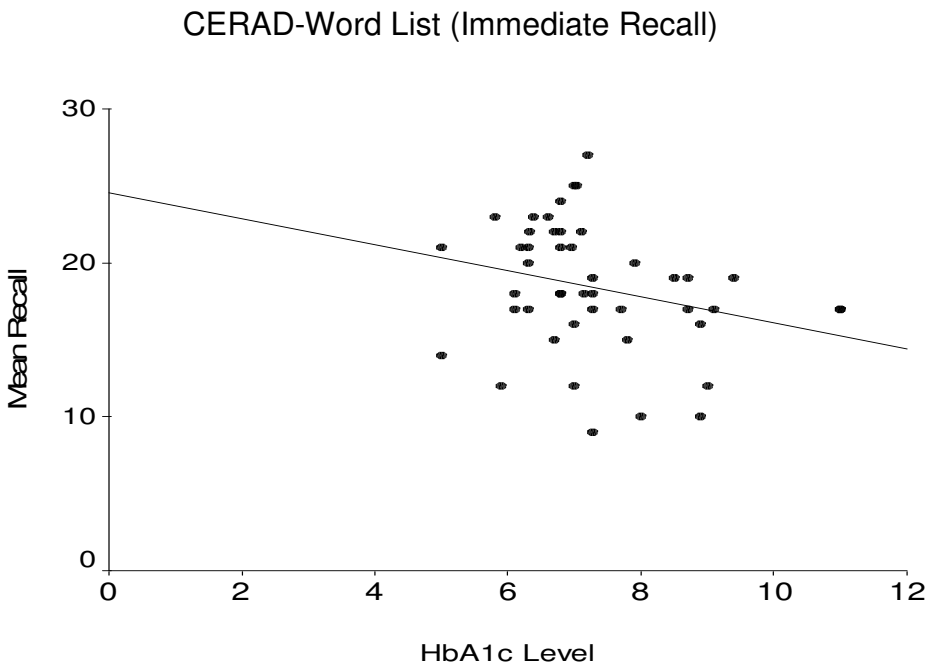

Figure 6. Significant decline on CERAD-WL recall with increasing HbA1c level among participants with Type 2 DM, p = .03.

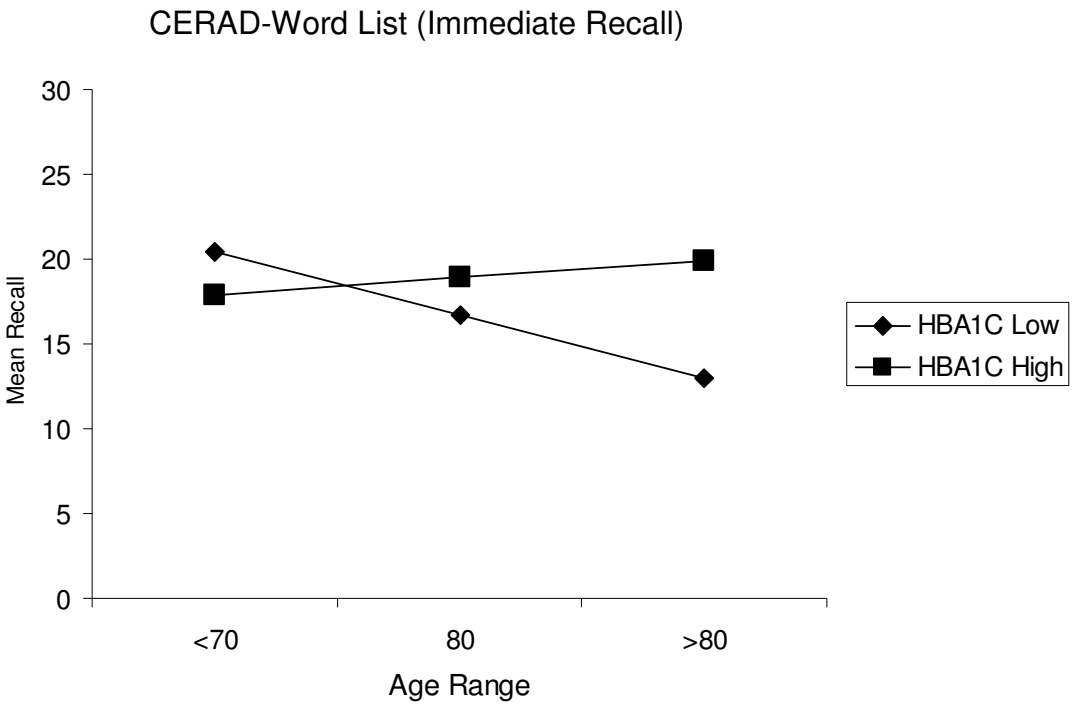

Figure 7. Significant Age by HbA1c interaction on CERAD-WL. Those with higher HbA1c performed worse than low in the younger Age range but improved with Age. The Low HbA1c recall declined with Age, $p = .00$.

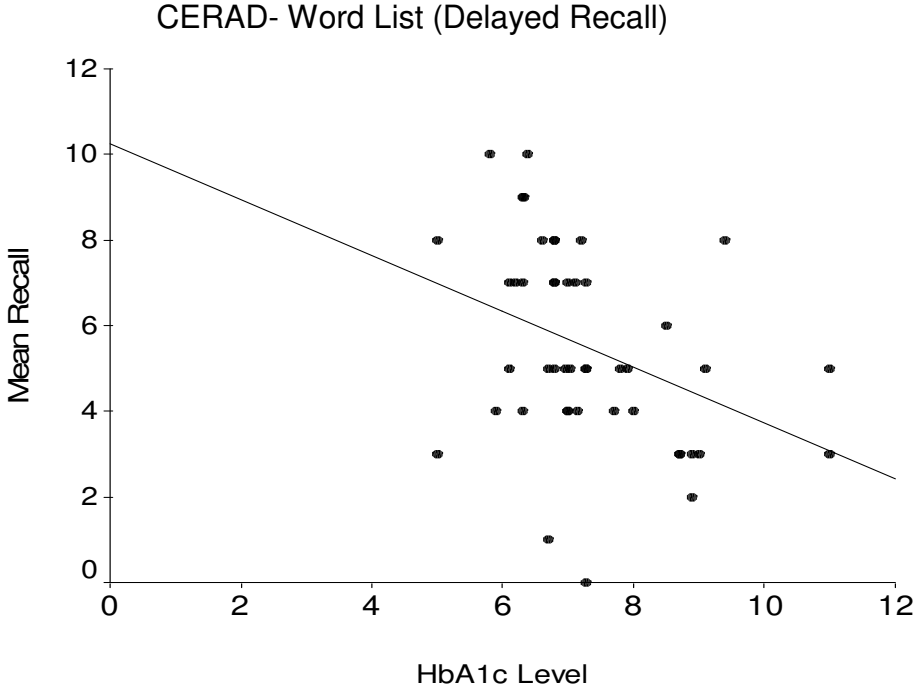

Figure 8. Significant decline on CERAD-WL delayed recall with increasing HbA1c level among participants with Type 2 DM, $p = .00$

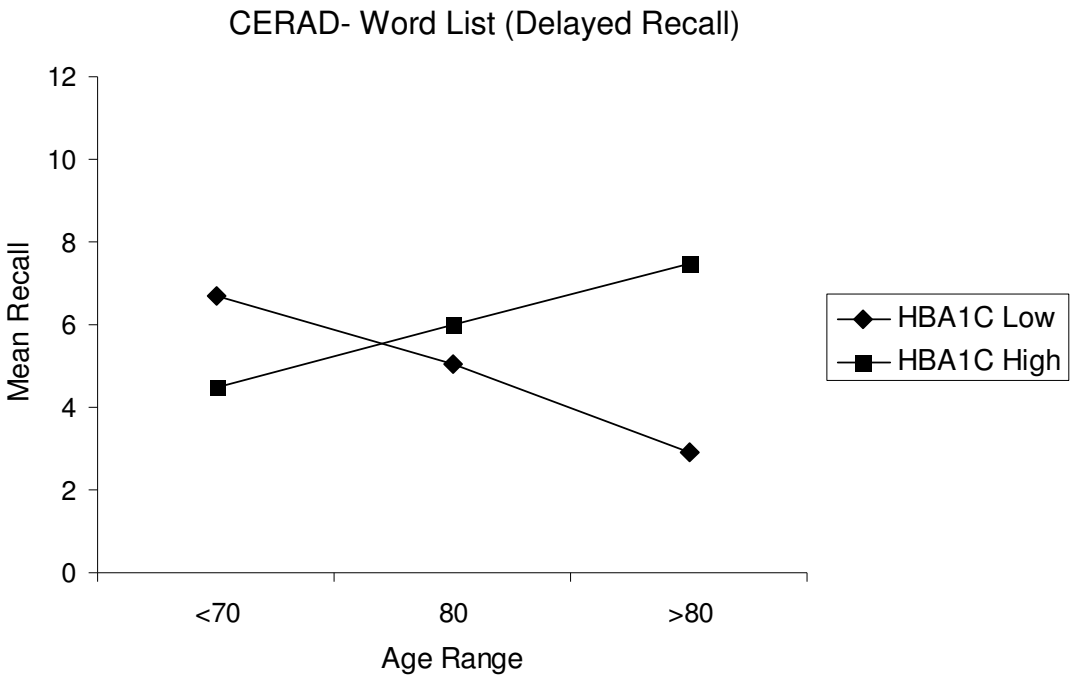

Figure 9. Significant age by HbA1c interaction on CERAD-WL delayed recall. Those with higher HbA1c performed worse than low in the younger age range but improved with age. The recall of those with low HbA1c declined with age, $p = .00$.

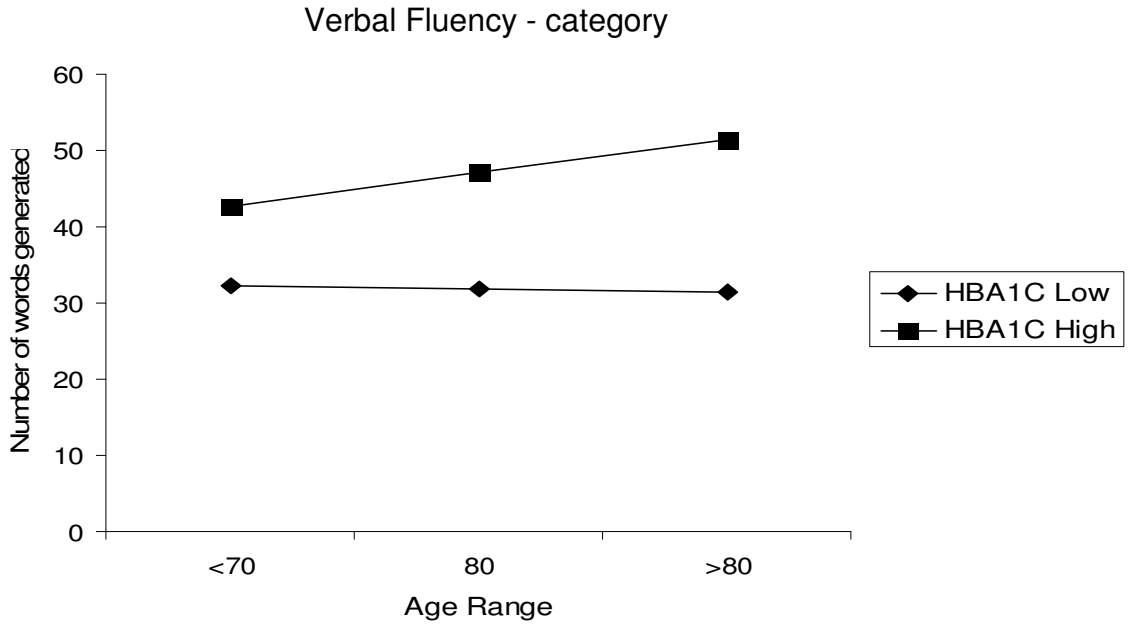

Figure 10. Significant Age by HbA1c interaction on Verbal Fluency. Those with higher HbA1c performed better than individuals with low HbA1c across all Age Groups. Those with high HbA1c improved with Age, whereas those with low HbA1c declined slightly, $p = .00$.

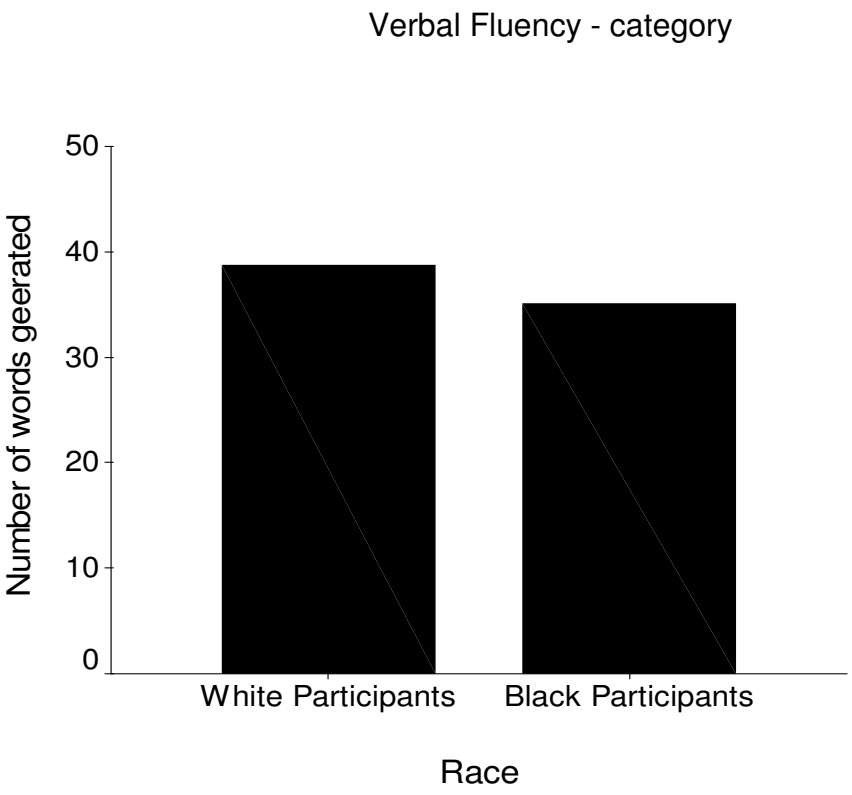

Figure 11. Significant relationship between Race and Verbal Fluency-category. Black participants with Type 2 DM generated fewer words than White participants, $p = .01$.

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