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Impaired Glucose Tolerance in Aging as a Risk Factor for Cognitive Dysfunction

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Abstract

Growing evidence suggests that impaired glucose tolerance may contribute to the development of cognitive dysfunction in otherwise healthy individuals (Neergard et al., 2017). The goal of this study was to clarify the relationship between pre-clinical insulin resistance, as estimated by plasma glucose levels, and cognitive functioning in older adults. It was hypothesized that glucose levels at the higher end of the normal range are associated with cognitive dysfunction and with differences in brain activation during a working memory task. Participants completed the Brief Cognitive Rating Scale (BCRS; Reisberg et al., 1988), Global Deterioration Scale (GDS; Reisberg et al., 1982), Mattis Dementia Rating Scale (MDRS; Mattis, 1988), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1988), Letter Number Sequencing Test (LNS; Wechsler, 2008), Cognitive Change Index (CCI; Saykin et al., 2006), Symbol Digit Modalities Test (SDMT; Forn et al., 2013), and the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001). A series of correlations between fasting glucose levels and cognitive test performance was computed. Fasting glucose levels were positively associated with BCRS and GDS scores but no other measures. In addition, an independent samples *t*-test comparing cognitive performance of the high glucose group (glucose ≥ 100 mg/dL) and low glucose group (glucose < 100 mg/dL) indicated performance differences in executive functioning and verbal fluency. BMI was an additional factor associated with cognitive dysfunction. This study and future studies with larger sample sizes may help to inform new blood glucose control guidelines in healthcare, as even the higher end of the normal blood glucose range may be associated with cognitive decline.

Introduction

The neurodegenerative conditions seen in aging populations represent a substantial social and economic burden on society. In light of the growing aging population, these age-related neurodegenerative disorders are expected to become more prevalent and are thus of increasing public concern (Zahra et al., 2020). Neurodegenerative disorders are characterized by a progressive reduction in most cognitive functions, which negatively affect a person's behavior, personality, social relationships, and can make it difficult to function in daily life (Dugger & Dickson, 2017). The development of these cognitive disorders, the most common being Alzheimer's disease, is thought to begin years or even decades prior to the clinical diagnosis of the disorder. Because diagnosis of these neurodegenerative conditions tends to occur late in the disease process, it is important to identify and address potential risk factors that may contribute to the development of cognitive dysfunction (Tarawneh & Holtzman, 2012).

One potentially modifiable risk factor that has been implicated in the development of cognitive dysfunction is insulin resistance. Insulin is a hormone that maintains glucose homeostasis in the periphery, but that also has numerous important functions in the brain (Cholerton et al., 2013). Disruption in insulin signaling commonly occurs in Type 2 diabetes, which is a disease that is characterized by insulin resistance. Insulin resistance is defined as the reduced sensitivity of cells to the effects of insulin and has been shown to be a risk factor for cognitive dysfunction (Ma et al., 2015). In light of the high prevalence of insulin resistance-associated conditions and their potential link to cognitive dysfunction, blood sugar control may be an important target for the prevention of cognitive decline (Meigs, 2003). Recent studies have indicated that even pre-clinical insulin resistance and impaired glucose tolerance may be associated with the early stages of cognitive decline (Laws et al., 2017). This study looked at the

effects of impaired glucose tolerance, as measured by fasting blood glucose levels, and cognitive performance in a sample of older adults.

Insulin is a peptide that is secreted by pancreatic beta cells to maintain glucose homeostasis. Maintaining optimal plasma glucose levels is critical to ensure that there is sufficient energy available for cellular metabolic processes. Insulin controls blood glucose concentrations by stimulating glucose transport into adipose and muscle tissue. Insulin also lowers blood glucose concentrations by inhibiting hepatic glucose production. More specifically, insulin molecules bind to cellular insulin receptors, which leads to a cascade of cellular events that in turn signal insulin-sensitive glucose transporters inside the cell to move to the membrane of insulin-sensitive peripheral tissue (Saltiel & Kahn, 2001). The activated glucose transporter promotes the use of glucose in the cells. Controlling glucose uptake becomes particularly important in the period following the ingestion of food, called the postprandial state. In the postprandial state insulin levels rise in order to promote the transport of glucose into the cells and lower blood glucose levels (Lefèbvre & Scheen, 1999).

Historically, insulin signaling was thought to be restricted to the periphery where it regulates glucose levels. The view that the brain is an insulin-insensitive organ was primarily informed by studies that found that glucose transport through the blood-brain barrier into the brain was not affected by insulin levels in the periphery. For example, Hasselbach et al. (1999) found that peripheral insulin concentrations were not correlated with blood-brain barrier glucose transport or net cerebral glucose metabolism in humans (Hasselbach et al., 1999). However, it is now known that there are two potential routes that allow peripheral insulin to reach the brain. Peripheral insulin can cross the blood-brain barrier through brain microvascular endothelial cell uptake (Banks et al., 2014; Gray et al., 2014). It can also flow directly into the cerebrospinal

fluid without having to cross the blood-brain barrier, because there are circumventricular regions that have porous capillaries instead of the typical blood-brain barrier (Gray et al., 2014). While the exact mechanisms and relative contributions of these two routes are unknown, it is thought that insulin that is actively transported through brain endothelial cells then mixes with insulin in the cerebrospinal fluid and eventually enters brain interstitial fluid (Gray et al., 2014). This theory is supported by studies that have found that peripheral insulin levels are correlated with the insulin levels found in cerebrospinal fluid (Levin et al., 2011). This provides evidence that peripheral insulin can cross the blood-brain barrier and reach brain tissue even though it does not significantly affect cerebral glucose metabolism.

Research over the past decade has shown that insulin has numerous effects in the CNS that are largely unrelated to the metabolic functions of insulin (Pomytkin et al., 2018). More specifically, insulin affects the areas in the brain involved in global cognitive and memory functions. It is an important regulator of synapse formation and synaptic plasticity in the hippocampus and in other brain regions involved in learning and memory (Baskin et al., 1987; Chiu & Cline, 2010; Levin & Sherwin, 2011). It also modulates the release of the neurotransmitters acetylcholine and norepinephrine, which both play a role in cognition (Cholerton et al., 2013). Insulin is also thought to serve as a neuroprotective agent. Studies have shown that it has antiapoptotic effects and that it can protect against beta amyloid toxicity, oxidative stress, and ischemia (Blazquez et al., 2014).

Due to the important role of insulin in these various cognitive functions, it is no surprise that disruptions in insulin signaling are associated with a higher risk for cognitive impairment and dementia compared to healthy controls with normal insulin signaling (Whitmer et al., 2008). Disruption in insulin signaling commonly occurs in Type 2 diabetes, which is a disease that is

characterized by insulin resistance. In insulin resistance, prolonged peripheral hyperinsulinemia causes insulin receptors to down regulate, rendering tissue unresponsive to insulin (Cholerton et al., 2013). Impairments in insulin signaling have been linked to the development of brain pathologies like Alzheimer's disease (Laws et al., 2017). The development of these cognitive dysfunctions in individuals with insulin resistance is thought to be triggered by hyperglycemic toxicity, chronic inflammatory processes, and mitochondrial dysfunction (Lee et al., 2016). Individuals with Alzheimer's disease have also been shown to have a reduction in neuronal insulin receptors, demonstrating that the desensitization of neuronal insulin receptors is related to Alzheimer's disease pathology (Hoyer, 2002; Cholerton et al., 2013). Another line of evidence for the role of insulin resistance in Alzheimer's pathology comes from studies that showed that insulin resistance disrupts amyloid beta plaque (Aβ) clearance and degradation (Ho et al., 2004). Aβ plaques are found in high concentrations in the brains of individuals with Alzheimer's disease and are thought to interfere with normal neuronal communication (Cholerton et al., 2013). Together, these findings suggest that insulin resistance may precipitate the pathological symptoms of Alzheimer's disease.

Moreover, studies have looked specifically at the relationship between insulin resistance and cognition in patients with Alzheimer's disease, with findings suggesting that an increase in insulin resistance is significantly associated with the clinical stages of Alzheimer's disease. The Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Aging investigated the relationship between insulin resistance and cognitive performance across several domains in cognitively normal patients and in patients with Alzheimer's disease. This study found that measures of insulin resistance were significantly higher in patients with Alzheimer's disease compared to cognitively normal patients. These findings indicate that insulin resistance may

contribute to the cognitive dysfunction seen in Alzheimer's disease. Furthermore, higher measures of insulin resistance were associated with poorer performance on cognitive measures in patients with Alzheimer's disease. Interestingly, even in cognitively normal individuals, increases in insulin resistance were still associated with reductions in global cognition (Laws et al., 2017). Findings from the Prospective Epidemiological Risk Factor Study (n = 2,103), a prospective study of older women in Denmark, suggested that subjects with impaired fasting plasma glucose and insulin resistance also have a higher probability of developing cognitive dysfunction. Fasting plasma glucose level was the single metabolic risk factor that was most strongly associated with cognitive dysfunction, with subjects having a 44% higher likelihood of cognitive dysfunction compared to normoglycemic subjects (Neergaard et al., 2017).

Given that Alzheimer's disease and Type 2 diabetes are both characterized by long prodromal periods, it is difficult to study the progressive relationship between the two (Laws, 2017). Thus, the association between the pre-clinical stages of diabetes and cognitive function in non-demented adults is less clear and remains understudied. One study looking at the disease progression of dementia found that the presence of pre-diabetes accelerated the cognitive decline in dementia patients (Xu, 2010). Another study had similar findings, indicating that features of insulin resistance were associated with Alzheimer's disease (Kuusisto et al., 1997). Other studies have indicated that impaired glucose tolerance even without diabetes is associated with impaired verbal fluency and memory (Kanaya et al., 2004; Vanhanen et al., 1998). However, more research is needed to examine this association between pre-clinical insulin resistance and cognitive dysfunction in non-demented adults.

In addition to Type 2 diabetes and Alzheimer's disease, changes in insulin signaling are also seen in normal aging processes. In fact, even in the absence of a major risk factor like obesity, older adults are at an increased risk of developing insulin resistance (Muller et al., 1996). High fasting blood glucose and insulin resistance can contribute to the progression of neurodegenerative diseases commonly seen in aging individuals. It is particularly important for older adults to identify and address potential risk factors like insulin resistance because modifying these factors at the earliest stage is critical for effective prevention of later cognitive decline. In light of the growing aging population, older individuals without diabetes but who are starting to show signs of insulin resistance likely represent a large population at additional risk for cognitive dysfunction, which have significant societal and economic impacts (Cowie et al., 2006).

The studies above outline the changes in cognition that can occur in individuals with insulin resistance and impaired glucose tolerance. However, there has been conflicting evidence regarding which specific cognitive domains are most affected by elevated blood sugar and other measures of insulin resistance. Laws et al. (2017) found that greater insulin resistance was associated with poorer performance on measures of episodic memory, executive function, and global cognition (Laws et al., 2017). Conversely, another study found that insulin resistance was only associated with deficits in verbal fluency (Benedict et al., 2012). The functional areas of the brain that are linked to verbal fluency performance are the frontal and temporal lobes, which are involved in memory processes. Reductions in memory functions (episodic memory, verbal memory, working memory, and visual retention), executive functioning, and psychomotor speed have been most consistently observed in individuals with Type 2 diabetes, making it likely that

those cognitive domains are also affected in the preclinical stages of diabetes (Palta et al., 2014; Kodl & Seaquist, 2008).

The findings of some studies have indicated that the cognitive profile associated with insulin resistance may be similar to that seen in normal aging processes, which affects areas such as processing speed, executive functioning, and attention (Salthouse, 1996; Craik et al., 2010). For instance, Yeung et al. (2009) found that healthy controls performed better than patients with Type 2 diabetes only on measures of executive functioning and processing speed (Yeung et al., 2009). These findings suggest that Type 2 diabetes may be associated with exacerbating the neurodegenerative processes seen in aging (Enzinger et al., 2005). However, it is also worth noting that not all studies have found an association between impaired glucose tolerance or Type 2 diabetes and cognitive performance (Scott et al., 1998; Kodl & Seaquist, 2008). More research is needed to further understand if and which cognitive domains are affected by pre-clinical insulin resistance.

The mixed results in the association between impaired glucose tolerance, insulin resistance and cognitive measures are also reflected in functional magnetic resonance (fMRI) studies looking at the effects of insulin resistance on brain functioning. Insulin resistance is thought to affect specific brain regions, primarily the hippocampus, the prefrontal cortex, and the cingulate gyrus. It is thought that a loss of functional connectivity of the default mode network in these regions may help to explain the cognitive dysfunction seen in type 2 diabetes, insulin resistance, and dementia (Kullmann et al., 2012). The default mode network refers to the baseline cognitive state of a subject that is active when one is awake but not involved in any specific mental task (Moheet et al., 2015). This network also involves brain regions that are

involved in attention and executive functioning. Interestingly, Alzheimer's disease and Type 2 diabetes have both been observed to have decreased functional connectivity of the posterior cingulate cortex in the default mode network (Musen et al., 2012; Greicius et al., 2003). High blood glucose has also been associated with impaired deactivation of the default mode network, indicating that impaired glucose tolerance may contribute to cognitive dysfunction (Marder et al., 2014).

In addition to alterations of the default mode network, fMRI studies have also indicated alterations in neural network activity during memory tasks in patients with Type 2 diabetes (Wood et al., 2016). For instance, Wood et al. (2016) found that the insulin resistance seen in Type 2 diabetes is associated with reduced activation in left hemisphere temporoparietal regions and greater activation in bilateral posteriorly distributed regions during a memory task, providing evidence that Type 2 diabetes is associated with memory related neuronal dysfunction (Wood et al., 2016). Other studies have found that patients with Type 2 diabetes exhibit hyperactivation of working memory-related brain circuits, which can be interpreted as being a compensatory brain activation due to brain inefficiency related to hyperglycemia (He et al., 2015).

Obesity is another factor that has been associated with both insulin resistance and cognitive dysfunction (Kahn & Flier, 2000; Qizilbash et al., 2015). Obesity is known to almost double the risk of Alzheimer's disease development and thus serves as an additional risk factor for cognitive dysfunction (Anstey et al., 2011). The most common way to assess if a patient is overweight or obese is to determine their body mass index (BMI), which is the weight of an individual in kilograms divided by the square of his or her height in meters. BMI has been

correlated with the development of Alzheimer's disease and other dementias, particularly in subjects with insulin resistance and Type 2 diabetes (Benito-Leon et al., 2013).

Because the interplay between aging, obesity, elevated fasting blood glucose levels, insulin resistance and cognitive dysfunction is complex it is often grouped together under the term "metabolic syndrome." Metabolic syndrome is defined as a collection of risk factors that increase your chance of developing heart disease, diabetes, stroke, and dementia (Saklayen, 2018). Even though there are many factors involved in this syndrome, prior research has shown that a decrease in insulin sensitivity in the central nervous system may represent a potential link between metabolic and cognitive dysfunction (Laws et al., 2017).

In sum, while it is well understood that Type 2 diabetes is a risk factor for dementia, more recent findings suggest that even non-clinically impaired individuals who are showing signs of insulin resistance and impaired glucose tolerance may also be at risk of cognitive dysfunction. Furthermore, reductions in cognition in individuals with elevated markers of insulin resistance have been identified in a handful of studies, but there has been conflicting evidence regarding which cognitive domains are most vulnerable to the effects of early blood glucose dysregulation and insulin resistance (Laws et al., 2017; Benedict et al., 2012; Palta et al., 2014). Lastly, most research linking blood glucose dysregulation and cognitive dysfunction has not been focused solely on older adults who may represent an at-risk population. Therefore, this study hoped to build on existing evidence to understand the impact of fasting blood sugar on cognitive function in individuals whose blood glucose levels are still in the normal range, but who we propose are at risk for cognitive dysfunction. This study had three hypotheses: 1) plasma glucose levels at the higher end of the normal range are negatively associated with cognitive

performance, 2) early cognitive processing stages are most affected in pre-clinical insulin resistance in a population of older adults, and 3) higher plasma glucose levels are associated with compensatory changes in brain activation during an fMRI working memory task.

Methods

Participants

Participants were 22 healthy, non-diabetic, non-obese adults, aged 50-75 years, *M*(*SD*)= 65.91(6.07). Of these participants, 16 were female and 6 were male. The mean level of education as measured by years of schooling was 16.39 years (*SD*=1.78) (see Table 1 for demographic information). Participants were recruited into two ongoing studies in the Dumas lab: One study focuses on the effects of fatty acids on brain functioning in older adults (DIET study) and the other study focuses on cognition after menopause and risk factors related to Alzheimer's disease (CHAMP study). In both studies, all participants completed cognitive and behavioral screenings at baseline, which are described in the following section.

Measures

This study included measures of physical health, cognitive and behavioral performance, neuropsychological performance, and functional magnetic resonance imaging (fMRI) during a working memory task. Fasting blood glucose levels and hemoglobin A1C measurements were obtained via a blood draw on study day 1 for the CHAMP study and on the pre-study day visit for the DIET study. Both measurements were obtained before any study specific manipulations occurred. Systolic and diastolic blood pressure, height, and weight were also taken on those days. Body mass index (BMI) was calculated. The psychiatric and neuropsychological measures used in this study are described below.

Psychiatric Evaluations

The Brief Cognitive Rating Scale (BCRS; Reisberg & Ferris, 1988) was used to assess functional and cognitive abilities in 5 different areas. These include concentration, recent memory, past memory, orientation, and functioning and self-care. It is commonly used in conjunction with the Global Deterioration Scale (GDS; Reisberg et al., 1982) that assessed the severity of cognitive impairment in patients. The Mattis Dementia Rating Scale (MDRS; Mattis, 1988) was used to assess the overall level of cognitive functioning. The MDRS measured performance in the domains of attention, initiation and perseveration, construction, conceptualization, and memory to assess cognitive changes associated with dementia. The Beck Depression Inventory (BDI; Beck et al., 1996) is a 21-item self-report instrument that was used to determine severity of depression in the participants. The Beck Anxiety Inventory (BAI; Steer et al., 1997) is a 21-item self-report instrument that was used to determine the presence and severity of anxiety symptoms in the participants. The Test of Premorbid Functioning (TOPF; Wechsler, 2011) was used to estimate pre-morbid memory and cognition. The Structured Clinical Interview for DSM-IV (SCID; First et al., 2015) is a diagnostic exam that was used to screen for Axis 1 psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

In order to exclude individuals with significant cognitive or behavioral impairments. Participants were required to have a MDRS score of greater than 123 and an estimated IQ of above 80. Participants were also excluded on the basis of having an untreated or unremitted psychiatric disorder as determined by the SCID, the BDI, and the BAI.

Neuropsychological Measures

The Cognitive Change Index (CCI; Saykin et al., 2006) self-questionnaire was used to measure self-perception of cognitive decline in the areas of memory, executive functioning, and

language domains. It is moderately related to objective test performance in those areas. The Symbol Digit Modalities Test (SDMT; Forn et al., 2013) was used to measure attention and processing speed. In the SDMT, participants were asked to complete a 90 second substitution task in which they had to pair numbers with geometric figures using a reference key. The Letter Number Sequencing (LNS; Wechsler, 2008) is a subtest on the Wechsler Adult Intelligence Scale used to measure verbal working memory. In the LNS, participants were asked to sequence a random order of numbers and letters. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998) is an individually administered battery that was used to measure cognitive decline or improvement across different cognitive domains. These cognitive domains included immediate memory, visuospatial/constructional, language, attention, delayed memory, and executive functioning tests. The Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) is a neuropsychological test that measured verbal and nonverbal executive functioning. It is composed of 9 subtests, however only the trail making test and the verbal fluency test were used in this study. The Trail Making Test is a visual-motor sequencing task that was used to measure cognitive flexibility and the Verbal Fluency Test was used to measure letter fluency, category switching, and category fluency.

fMRI N-back Task

The *n*-back task is a widely used, reliable measure of working memory performance. It reliable activates bilateral frontal, parietal, and cerebellar working memory networks (Meule, 2017). The *n*-back task involved participants attending to a series of stimuli and responding whenever a stimulus is presented that is the same as the one presented *n* trials before. Participants were shown a series of consonant letters (except L, W, and Y), one for every three

seconds. There were four different conditions that were presented to the participants: 0-back, 1-back, 2-back, and 3-back. In each of the conditions, participants decided whether the currently presented letter matched the letter that was presented *n*-trials back in the sequence. If the participant believed that it matched, they pressed a match button; if they did not believe that it matched, they pressed a mismatch button. Participants were given two practice rounds of each of the four different conditions on a computer before completing the *n*-back task in the MRI scanner. The accuracy and reaction times were recorded for each of the trials (Meule, 2017).

fMRI Data Acquisition and Processing

fMRI data was obtained after the first week of controlled diet in the DIET study and on study day 1 in the CHAMP study. The Philips 3T Achieva d-Stream MRI scanner used in this study was located at the UVM MRI Center for Biomedical imaging at the University of Vermont Medical Center. The MRI imaging protocol used was developed for the multicenter NIH-funded Adolescent Brain Cognitive Development (ABCD) study and includes simultaneous multi-slice imaging, called MultiBand SENSE. MultiBand SENSE acquisition schemes allow the acquisition from more than one spatial coordinate at a time and thus can accelerate functional MRI acquisitions (Setsompop et al., 2012). The structural MRI acquisition was comprised of T1 and T2 weighted images that had an isotropic resolution of 0.8mm and a T2-FLAIR isotropic resolution of 1.0mm. The task and resting state fMRI parameters were TR 800ms, TE 35ms, flip angle 52 degrees, 2.4mm isotropic imaging resolution with a $216\times216\times144mm^3$ field of view using a multiband acceleration factor of 6 (60 slices, no gap). MRI images reviewed by a neuroradiologist in order to exclude intracranial pathology.

fMRI was performed using EpiBOLD (echoplanar blood oxygenation level dependent) imaging using a single-shot sequence (TR 800 ms, TE 35 ms, flip angle 90 degrees, 1 NSA for

615 volumes). Resolution was 1.8 mm x 1.8 mm x 1.8 mm. Sixty contiguous slices 1.8 mm thick with no gap were obtained in the axial oblique plane parallel to the AC-PC plane using a FOV of 240 mm and a matrix size of 80 × 80. Field map correction for magnetic inhomogeneities was accomplished by acquiring images with offset TE at the end of the functional series (Dumas et al., 2018).

fMRI Analyses

Structural and fMRI preprocessing used standard procedures implemented in the Dumas Lab similar to prior published fMRI work (Dumas et al., 2010; Dumas et al., 2012; Dumas et al. 2019). These included realignment of volumes to the first volume to minimize the effects of head movements, as well as spatial and temporal filters to remove aliased signal correlated to background respiration and heart rate. The anatomical and functional images were also co-registered and normalized to Talairach space. We performed a multisubject analysis in Brain Voyager QX. We used multiple linear regression of the signal time course at each voxel to estimate the hemodynamic response. We chose to focus our image-based analysis on the 2-back minus 0-back contrast. Given the small sample available for the imaging analysis, we did not compute any corrections for multiple comparisons.

Statistical Analyses

The primary goal of this study was to examine the relationship between pre-clinical insulin resistance, as estimated by fasting blood glucose levels, and performance on a variety of cognitive measures using Pearson's correlations in SPSS. Next, participants were divided into a high fasting blood glucose group (fasting blood glucose level ≥ to 100 mg/dL; clinically categorized as prediabetes) and a low fasting blood glucose group (fasting blood glucose level < 100 mg/dL). Independent samples *t*-tests were performed to assess whether participants in the

high fasting blood glucose group performed differently from the low fasting blood glucose group. Additional correlational analyses were performed in order to evaluate whether secondary factors, including sex, BMI, A1C levels, diastolic and systolic blood pressure, and level of education, were associated with performance on each cognitive test. To examine the relationships between fasting blood glucose and BOLD signal from clusters activated in the working memory task, we performed a Pearson's correlation. We also performed a Pearson's correlation between BMI and BOLD signal from the activated clusters from the *n*-back task.

Results

Cognitive Test Performance

We found that higher fasting blood glucose levels were positively correlated with BCRS (r= 0.64, p= 0.001) and GDS scores (r= 0.64, p= 0.001). Fasting blood glucose levels were not correlated with performance on the other cognitive measures. The independent samples t-test using high and low glucose groups found that there were differences between the Initiation/Perseveration domain of the MDRS for the high glucose (M= 11.20, SD= 0.42) and low glucose (M= 10.29, SD= 1.25) groups; $t(15)$= 2.16, p= 0.047. There was also a difference in the language domain of the RBANS scores for the high glucose (M=104.23, SD= 8.16) and low glucose (M= 97.60, SD= 5.89) groups; $t(20)$= 2.15, p= 0.044.

Additional correlational analyses found that BMI was negatively correlated with performance on the RBANS (see Figures 1-3). Specifically, BMI was negatively correlated with RBANS total score (r= -0.61, p= 0.003), RBANS delayed memory (r= -0.63, p= 0.002), and RBANS attention (r=-0.59, p= 0.005). Sex, age, A1C, level of education, diastolic blood pressure, and systolic blood pressure were not correlated with performance on any of the cognitive measures.

fMRI Activation Data

We examined working-memory related brain activation in the *n*-back task in seven of the participants for whom we had imaging data. When we compared the 2-back working memory load condition to the 0-back condition, we found the expected bilateral frontal, parietal, and cerebellar working memory network to be activated (Cohen, 1997). To test our hypothesis that higher levels of fasting blood glucose influenced brain functioning during a working memory task, we performed a Pearson's correlation between fasting blood glucose levels and BOLD signal from clusters activated during the N-back task in the expected working memory regions. We found that fasting blood glucose levels were correlated with activation in the right angular gyrus in the parietal lobe (Brodmann area 39) during the 0-back condition *(r*= 0.85, *p*= 0.016) and the 2-back condition *(r*= 0.78, *p*= 0.037) (See Table 2). We also found that BMI was correlated with activation in the left premotor and supplemental motor area (Brodmann area 6) during the 1-back condition *(r*= 0.85, *p*= 0.015) (see Table 2).

Discussion

There is a growing literature examining the effects of Type 2 diabetes, insulin resistance, and impaired glucose tolerance on cognition in older adults. We contribute to this literature by examining the impact of fasting blood sugar on cognitive function in older adults whose fasting blood glucose levels were not yet clinically elevated. Our first hypothesis was that fasting blood glucose levels at the higher end of the normal range would be negatively correlated with cognitive performance, particularly on measures of early cognitive processing stages. Results of our correlational analyses showed that higher fasting blood glucose levels were positively associated with BCRS and GDS scores, which are both clinician ratings of cognitive functioning. The BCRS and GDS are used to stage a person who is showing signs of a dementia such as

Alzheimer's disease, with higher scores indicating more adverse changes in cognition (Reisberg & Ferris, 1988; Reisberg et al., 1982). Importantly, these measures are sensitive to a person's subjective complaints of cognitive decline. Subjective cognitive decline refers to when a person feels that they are cognitively impaired but do not yet show objective deficits in cognitive test performance. The presence of subjective cognitive complaints is thought to be an early clinical marker of dementia as it has been shown to precede objective cognitive deficits (Parfenov et al., 2020). Thus, our findings suggest that elevated fasting blood glucose measures may be affecting the early stages of cognitive decline in which a person experiences a subjective deficit in cognition before any objective changes in performance are observed. However, it is worth noting that we did not find the expected correlation between fasting blood glucose and performance on the CCI, which is a subject-reported measure of subjective cognitive decline. There was also little variance in BCRS and GDS scores due to our small sample size, indicating the need for future studies to ensure the validity of our results.

Fasting blood glucose was not correlated with performance on any of our other cognitive measures. In particular, we did not find reductions in global cognition, as measured by the RBANS total and MDRS total. Global cognition refers to the overall level of cognitive functioning of an individual. Our results stand in contrast to prior research that had found that increases in insulin resistance were associated with reductions in global cognition in cognitively normal adults (Laws et al., 2017; Kong et al., 2018). One way to interpret these results is that the cognitive profile of pre-clinical insulin resistance as estimated by elevated blood glucose levels was seen in domain-specific cognitive impairments rather than in measures of global cognition. These findings are supported by other studies that found that insulin resistance mainly affects the

attention, executive function, and processing speed, which may not be accurately assessed using only measures of global cognition (Yeung et al., 2009).

The results of the independent samples *t*-test showed that there were significant differences in performance between participants in the high fasting blood glucose (blood glucose level ≥ to 100 mg/dL; clinically categorized as prediabetes) and low blood glucose groups (blood glucose level < 100 mg/dL) on the Initiation/Perseveration (I/P) domain of the MDRS. The I/P domain of the MDRS is a composite measure of several executive skills (Mattis, 1988). Given that insulin resistance has been shown to affect executive functioning, it is likely that executive function is also affected in the pre-clinical stages of insulin resistance (Schuur et al., 2010; Abbatecola et al., 2004). Thus, the results of our study supported that those effects on executive functioning may even be seen in patients who are not yet clinically impaired. However, it is worth noting that we did not find significant group differences in performance on the DKEFS, which is another measure of executive function. Furthermore, the results of our correlational analyses did not show significant correlations between fasting blood glucose and measures of executive functioning.

There was also a difference in performance on the language domain of the RBANS between the high glucose and low glucose groups. The language domain of the RBANS is primarily a measure of verbal fluency, which includes phonetic and semantic fluency. Verbal fluency is commonly thought of as being another measure of executive function. Insulin resistance has been associated with poorer verbal fluency in multiple studies: One study found that insulin resistance predicted poorer verbal fluency and a steeper decline in verbal fluency (Eklbad et al., 2017), whereas another found that insulin resistance was associated with poorer verbal fluency in women in particular (Ekblad, 2015). Interestingly, verbal fluency is also

commonly affected in Alzheimer's dementia (Weakley, 2014). However, our findings suggest the opposite pattern as it was the high fasting blood glucose group who had better verbal fluency performance compared to the low fasting blood glucose group. We did not see these significant group differences on any of the verbal fluency measures of the DKEFS. Correlational analyses also did not show a relationship between measures of verbal fluency and fasting blood glucose levels. Given these discrepancies, more research is needed to observe if this pattern between fasting blood glucose and verbal fluency remains true in large sample sizes.

In addition to examining performance on a variety of cognitive tests, we also looked at brain activation during an fMRI working memory task. Our hypothesis was that higher fasting blood glucose levels would be correlated with compensatory changes in brain activation during the *n*-back task. As expected, we found the bilateral frontal, parietal, and cerebellar working memory network to be activated during the *n*-back task (Cohen, 1997). We also found that fasting blood glucose levels were correlated with increased activation in the right angular gyrus in the parietal lobe during the 0-back condition and the 2-back condition. The angular gyrus plays a key role in verbal working memory and is activated during the retrieval of verbal information (Seghier, 2013). One way to interpret these findings is that greater brain activation in the 2-back condition, as estimated by increases in the fMRI BOLD signal, was associated with decreased neural efficiency during the retrieval part of the working memory task. This view is consistent with prior neuroimaging studies that have shown that increased brain activation in working memory regions is associated with less efficient thinking patterns (Neubauer & Fink, 2009).

It is also interesting to note that the angular gyrus is part of the default mode network, which has recently been implicated as playing a role in working memory processes (Piccoli et

al., 2015; Koshino et al., 2014). Additionally, hyperglycemia has been associated with impaired deactivation of the default mode network (Marder et al., 2014). Thus, it is possible that hyperglycemia may contribute to brain abnormalities particularly affecting the default mode network. Although task-related activation in the right angular gyrus was associated with fasting blood glucose in our study, our results can only be interpreted in a preliminary manner because we were unable to correct for multiple comparisons in the small number of participants for whom we had imaging data for at this time. Correcting for multiple comparisons is important in order to minimize false positives and identify areas of brain activity that reflect true effects (Han & Glenn, 2018). Thus, further studies with larger sample sizes that correct for multiple comparisons are needed to verify if there are any changes in brain activation associated with elevated fasting blood glucose levels during a working memory task.

Secondary analyses showed that that BMI was negatively correlated with performance on the RBANS total, as well as with performance on the RBANS attention RBANS delayed memory. These findings support the idea that obesity is an additional risk factor for cognitive dysfunction. In fact, studies that have found that BMI is correlated with the development of Alzheimer's disease and other dementias, particularly in subjects with insulin resistance (Benito-Leon et al., 2013). We also found that BMI was correlated with activation in the left premotor and supplemental motor area during the 1-back condition of the *n*-back task. This finding indicates that BMI may also be associated with less efficient thinking patterns during a working memory task. Due to the complex interactions between the many factors associated with metabolic syndrome, it is difficult to make definitive conclusions about their temporal relationships. Thus, our results show that obesity may be an additional factor mediating the relationship between insulin resistance, hyperglycemia, and cognitive dysfunction.

Limitations

There are several limitations of this study to consider. One major limitation of this study is its small sample size (n=22). Because the expected association between high-normal fasting blood glucose and cognitive performance is relatively small compared to the association between clinically elevated fasting blood glucose and cognitive performance, our study may not have had the statistical power to expose such a small effect. Thus, future studies with larger sample sizes are needed to confirm that the results of our study are not due to chance.

Another limitation of this study was that we used fasting blood glucose levels to estimate the degree of insulin resistance in the participants. While elevated fasting blood glucose is a strong indicator of insulin resistance, it is not a direct measurement of insulin resistance. In other words, it is important to keep in mind that plasma glucose levels and insulin resistance are related but not equivalent concepts. There are factors in addition to insulin resistance, such as decreased insulin secretion, age, and triglycerides that may have affected the fasting blood glucose levels of the participants (Nishi et al., 2005; Aoyama-Sasabe et al., 2014). Thus, future studies that are able to utilize more accurate assessments of insulin resistance are needed to confirm our findings. Possible indexes for insulin resistance include the Homeostasis Model Assessment (HOMA) and the Quantitative Insulin Sensitivity Check Index (QUICKI), which both take into account fasting insulin and fasting glucose levels to estimate the degree of insulin resistance (Muniyappa & Madan, 2018).

Lastly, the outcomes of this study indicate a relationship between elevated fasting blood glucose and cognitive performance in specific areas, but we cannot demonstrate cause and effect due to the cross-sectional nature of our study. While there are studies that support the idea that hyperglycemia and insulin resistance precipitate the symptoms of cognitive dysfunction, we

cannot exclude the possibility that the early CNS defects associated with cognitive dysfunction are what give rise to metabolic dysfunction. In addition to this possibility, it is likely that there are additional factors mediating the relationship between insulin resistance and cognitive dysfunction. Our study addressed the effects of aging and obesity on both insulin resistance and cognition. Other factors that were not addressed but that fall under the category of metabolic syndrome risk-factors include hypertension, dyslipidemia, abdominal obesity, and impaired cerebral vasculature (Panza et al., 2010).

Conclusions

In summary, the results of this study indicate that fasting blood glucose levels at the higher end of the normal range may still negatively impact cognition in older adults, particularly seen in measures of subjective cognitive functioning and executive functioning. Preliminary fMRI imaging data also indicates the need for future research examining if there are any changes in brain activation associated with elevated fasting blood glucose levels during memory tasks, as this may be indicative of decreased neural efficiency in this population. Future studies with larger sample sizes are needed to better understand the relationship between impaired glucose tolerance, insulin signaling, and cognitive dysfunction in older adults. Given that dementia and Type 2 diabetes are both characterized by long prodromal periods, it is particularly important to identify and address risk factors early to prevent disease progression. The outcome of this study and additional studies may help to inform new blood glucose control guidelines in healthcare, as even the higher end of the normal blood glucose range may be associated with cognitive decline.

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Table 1. Demographic data and fasting blood glucose levels, BMI, A1C, systolic and diastolic blood pressure (means and standard deviations) for all study participants (n=22).

	Mean	Std. Deviation
Age	65.91	6.07
Educ	16.39	1.78
Glucose	101.41	14.20
BMI	26.61	4.44
A1C	5.58	.31
Systolic BP	127.52	25.76
Diastolic BP	71.22	12.78

Table 2. Brain activation clusters correlated with fasting blood glucose and BMI, respectively, during the 2-back minus 0-back condition of the *n*-back task. Includes Talairach coordinates, region descriptions (Brodmann's area, BA), *t* values, and *p* values.

Contrast	**Coordinates (x,y,z)**	**Region Description**	***t*-value**	***p*-value**
2-back minus 0-back (Correlated with fasting blood glucose levels)	40, -53, 39	Right angular gyrus (BA 39)	7.11	<0.001
2-back minus 0-back (Correlated with BMI)	-25, 5, 53	Left premotor /supplemental motor area (BA 6)	6.30	<0.001

Figure Legends

Figure 1. Relationship between BMI and scores on the RBANS total scaled (r=-0.610, p=0.003).

Figure 2. Relationship between BMI and scores on the RBANS attention (r=-0.585, p=0.005).

Figure 3. Relationship between BMI and scores on the RBANS delayed memory (r= -0.634, p=0.002).

Figure 4. Activation map for the n-back task comparing the 2-back minus the 0-back in the left premotor and supplemental motor area (Brodmann Area 6). Red colors represent increasing activation for the 2-back compared to the 0-back condition and blue colors represent decreasing activation for the 2-back compared to the 0-back condition.

Figure 1.

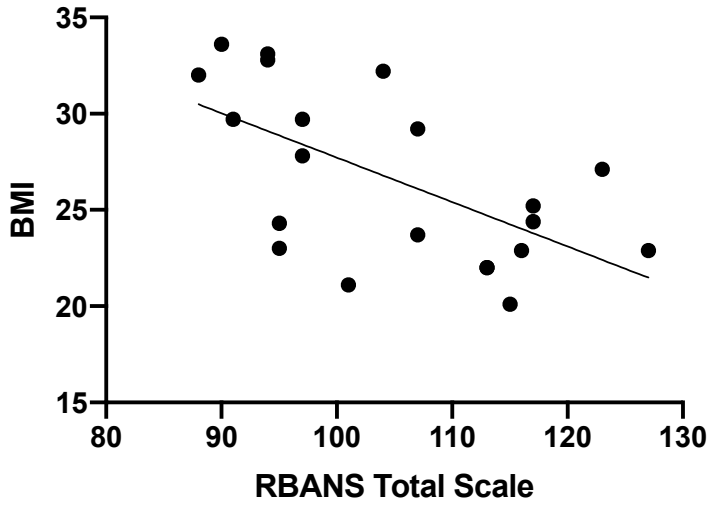

Figure 2.

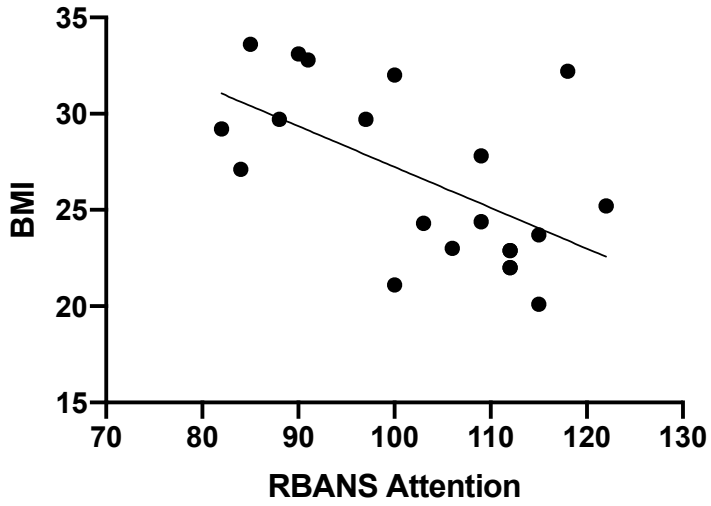

Figure 3.

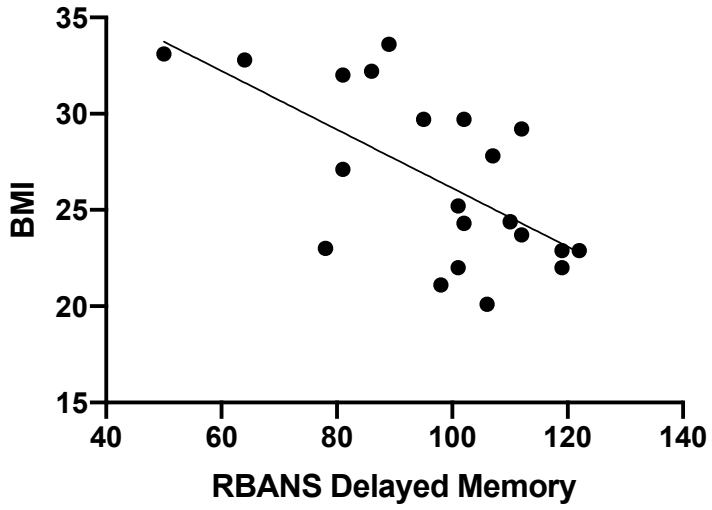

Figure 4.