The Effect of Glucose Regulation on Cognitive Functioning in a Healthy Sample of Older Adults

by

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Abstract

Type II diabetes and impaired glucose tolerance (IGT) are both associated with cognitive impairment and an increased risk of dementia, and normal aging has been shown to be accompanied by abnormalities in glucose regulation. The present study was conducted to determine if variations in cognitive performance would be observed as a function of glucose regulation in a healthy elderly population. Thus, cognitive functioning was measured in 93 healthy male and female older participants who ranged in age from 55 to 88. Participants had a glucose tolerance tests from which several biological indices were obtained including various glucose and insulin measures, and were separated into better and poorer glucoregulatory groups on the basis of these indices. Participants underwent two cognitive testing sessions, one after drinking a saccharin solution and another after drinking a glucose solution (50g). Participants with worse glucose regulation performed worse on measures of working memory, executive function, and processing speed compared to participants with better glucose regulation. Additionally, older participants with worse glucose regulation obtained the lowest scores on the majority of cognitive measures compared with younger participants and those with better regulation. A significant enhancement of cognitive performance by glucose was not clearly observed. The results suggest that cognitive functioning may be compromised before glucoregulatory impairment reaches levels consistent with IGT or Type II diabetes.

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As a part of the normal aging process, many individuals will experience declines in cognitive functioning. Memory (i.e, the acquisition and retrieval of new information), working memory, and information processing speed (Craik, Anderson, Kerr, & Li, 1995; Craik, 1994; Gold & Stone, 1988; Lezak, 1995; Winocur, 1988) are the areas of cognitive functioning that are typically affected. Although this age-related decline is considered normal, cognitive impairment is a major determinant of quality of life in aging. It is therefore important to identify the risk factors for cognitive impairment in order to gain an understanding of the causes of such impairment and to determine what may potentially lead to the reduction of risk factors (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995). Abnormalities in glucose regulation have been hypothesized to be one potentially modifiable risk factor for age-related cognitive impairment.

Glucose regulation is variable in the healthy population and normal aging has been shown to be accompanied by abnormalities in glucose regulation (Kent, 1976; Lipson, 1986) including elevated blood glucose levels (Levin, 1982; O'Sullivan, 1974) and decreased glucose utilization (Gold & Stone, 1988) both peripherally (Fink, Kolterman, Griffin, & Olefsky, 1983) and centrally (Kuhl, Metter, Riege, & Hawkins, 1984). Glucose is common in the human body, and is the main fuel used by the brain to function. It must be continually available to the brain to ensure optimal neuropsychological performance (Raichle, Herscovitch, Mintun, Martin, & Powers, 1984). Given that both the prevalence of memory problems and impaired glucose regulation increase with age (Shimokata, Muller, Fleg, Sorkin, Ziemba, & Andres, 1991; Unverzagt, Gao, Baiyewu, Ogunniyi, Gureje, Perkins, Emsley, Dickens, Evans, Musick et al., 2001), it has been hypothesized that abnormalities in glucose regulation may be

partially responsible for age-related declines in cognition (Gold, 1987; Korol & Gold, 1998).

Whereas individuals with excessive blood glucose levels are diagnosed with Type II diabetes, those with moderately elevated blood glucose levels are diagnosed with impaired glucose tolerance (IGT) (American Diabetes Association, 2002). Although not all cases of IGT will necessarily progress to a diabetic state, prolonged glucose tolerance impairment usually precedes a Type II diabetes diagnosis. The impact of Type II diabetes on cognitive function has been studied extensively (Biessels, Kappelle, Bravenboer, Erkelens, & Gispen, 1994; Strachan, Deary, Ewing, & Frier, 1997; Strachan, Frier, & Deary, 2003) and numerous studies have observed that a variety of cognitive impairments are associated with Type II diabetes in older individuals. Findings from population studies have also show that IGT is not only associated with, but is also a significant predictor of cognitive impairment in aging (Vanhanen, Koivisto, Kuusisto, Mykkanen, Helkala, Hanninen, Riekkinen, Soininen, & Laasko, 1998). Thus, it has been suggested that glucose regulation may influence the efficiency of cognitive functioning in both young (Messier, Desrochers, & Gagnon, 1999) and older individuals (Kaplan, Greenwood, Winocur, & Wolever, 2000; Messier, Gagnon, & Knott, 1997).

Despite the findings of cognitive decrements in individuals with Type II diabetes and the preliminary research indicating similar deficits in individuals with IGT, the course and nature of cognitive impairments associated with impaired glucose regulation remain equivocal. This may be due to the fact that numerous studies examining cognitive impairment in Type II diabetes are confounded because they do not take into account the various conditions that are associated with diabetes of a non-vascular (e.g., depression)

and vascular nature (e.g., hypertension, stroke) that have been independently shown to have an impact on cognitive functioning (Dufouil, Fuhrer, Dartigues, & Alperovitch, 1996; Waldstein, Manuck, Ryan, & Muldoon, 1991). Thus, some researchers have suggested that abnormalities intrinsic to Type II diabetes may not be responsible for a substantial portion of the cognitive decrements observed in Type II diabetes (Cosway, Strachan, Dougall, Frier, & Deary, 2001). Additionally, there is considerable methodological variability in the literature with regards to the neuropsychological and glucoregulatory measures utilized and the specific populations being evaluated.

Numerous studies have also demonstrated that cognitive functioning (particularly memory) improves following the ingestion of glucose in healthy individuals, with the most robust effects observed in individuals with poor glucose regulation (Greenwood, 2003; Kaplan et al., 2000, Messier et al., 1997; Messier et al, 1999). This suggests that increased blood glucose could overcome impaired glucose uptake in particular brain regions. However, Greenwood, Kaplan, Hebblethwaite, & Jenkins (2003) recently showed that acute ingestion of glucose in Type II diabetics does not result in memory improvement and in fact, contributes to further impairments to memory. Thus, glucose improvement of memory may be limited to non-diabetic individuals only.

The proposed research will examine the impact of glucose regulation on cognitive performance in a large sample of healthy older adults using a comprehensive battery of neuropsychological measures and several biological indices of glucose regulation (i.e., glucose tolerance, insulin, cholesterol, c-peptide) while controlling for a number of confounding variables, as will be discussed further in the introduction. Specifically, the research will examine whether progressive glucoregulation impairment leads to

progressive cognitive impairment, whether age interacts with glucose regulation to affect performance on neuropsychological measures, and finally, whether glucose ingestion improves performance on neuropsychological performance differentially with respect to glucoregulatory status in healthy older adults.

Given that the majority of research examining the effect of glucose regulation on cognition has focused on diabetic populations, the literature on Type II diabetes and its association with neuropsychological impairment and dementia will be reviewed prior to examining the extant literature on the impact of IGT, glucose regulation, and glucose ingestion on cognitive functioning. The mechanisms by which Type II diabetes, IGT, and glucose regulation may affect cognition are presently unknown although many hypotheses have been posited. Although elucidating these mechanisms is beyond the scope of the present proposal, a brief review of this literature will be provided.

Type II diabetes and Neuropsychological Impairment

Type II diabetes is one of the most common serious metabolic disorders in humans (Biessels et al., 1994). It is characterized by hyperglycemia resulting from insulin resistance and relative insulin deficiency (Biessels, van der Heide, Kamal, Bleys, & Gispen, 2002; Motta, Sorace, Restuccia, Carnazzo, Corrao, Seminara, & Maugeri, 1996). It typically occurs later in life (Bent, Rabbit, & Metcalfe, 2000) with an average age of onset of 60 years (Ryan, 2002). It affects up to 18% of women and 20% of men 65 years and older (Harris, Flegal, Cowie. Eberhardt, Goldstein, Little, Wiedmeyer, & Byrd-Holt, 1998). The risk of developing Type II diabetes is increased by several factors including age, obesity, an increased percentage of body fat situated in the abdominal region, and a lack of physical exercise (American Diabetes Association, 2002). The

prevalence of Type II diabetes is dramatically increasing worldwide as a result of population aging and lifestyle changes (King, Aubert, & Herman, 1998).

There are a number of vascular and neurological complications of hyperglycemia associated with Type II diabetes including nephropathy, angiopathy, retinopathy, and peripheral and autonomic neuropathy (Elias, Elias, D'Agostino, Cupples, Wilson, Silbershatz, & Wolf, 1997; Greene, Lattimer, & Sima, 1987; Strowig & Raskin, 1992; Worrall, Moulton, & Briffet, 1993; Zaslavsky, Gross, Chaves, & Machodo, 1995). Type II diabetes is also associated with an increased prevalence of a range of other conditions such as hypertension, stroke, hyperlipidemia, macrovascular disease, ischemic heart disease, depression, and cardiovascular disease (Cosway et al., 2001; Elias et al., 1997; Elliot & Viberti, 1993; Jarrett, 1989; McCall, 1992; Stegmayr & Asplund, 1995). As mentioned previously, it has been debated whether the cognitive decrements observed in Type II diabetes are primarily caused by these associated disorders rather than Type II diabetes per se (Colsher & Wallace, 1991; Harris, Deary, Harris, Lees, & Wilson, 1996; Kuusisto, Koivisto, Mykkanen, Helkala, Vanhanen, Hanninen, Pyorala, Riekkinen, & Laasko, 1993; Tun, Perlmurter, Rosso, & Nathan, 1987; Wahlin, Nilsson, & Fastbom, 2002). Contrary to this suggestion, a recent study showed that improvement of glucose regulation in diabetic patients was associated with improved cognitive functions (Ryan, Freed, Rood, Cobitz, Waterhouse, & Strachan, 2006).

McCall (1992) has suggested that Type II diabetes affects the brain in several ways by changing blood flow and brain metabolism, and increasing both the risk of and damage due to stroke. Furthermore, subtle, neurochemical, electrophysiological and structural changes have been found in the brains of individuals with Type II diabetes

(Biessels et al., 1994; McCall, 1992; Mooradian, 1988). A recent study observed that Type II diabetes was associated with white matter lesions, cortical and subcortical atrophy, and infarcts (Manschot, Brands, van der Grond, Kessels, Algra, Kappelle, & Biessels, 2006). Related to this structural and functional organ and tissue damage, there is now a large body of evidence that suggests that Type II diabetes is associated with cognitive impairment and dementia in older adults (Biessels, 1999; Messier & Gagnon, 1996; Strachan et al., 1997; Stewart & Liolitsa, 1999).

Strachan et al (1997) conducted a review of 19 studies examining the impact of Type II diabetes on cognitive functioning, the majority of which were cross-sectional case-control studies with small sample sizes. Of the 19 studies reviewed, 13 studies reported that individuals with Type II diabetes showed decreased cognitive functioning compared with non-diabetic controls. Specifically, 9 of 13 studies showed that a deficit was present in verbal declarative memory, 5 of 10 studies demonstrated a deficit in visuospatial memory, 3 of 11 studies reported a deficit in attention/concentration, and 3 of 8 studies observed a frontal lobe/executive functioning deficit. Thus, it was concluded that moderate cognitive impairment was shown by diabetic subjects in the domain of verbal declarative memory with executive function, attention/concentration, and visuospatial memory less commonly affected.

Since the review by Strachan et al. (1997), numerous well-controlled population-based studies, larger cross-sectional studies, and some prospective longitudinal studies have been conducted in this area. The majority of studies have observed that older individuals with Type II diabetes demonstrate reduced performance on various neuropsychological measures compared with individuals without Type II diabetes (Bent

et al., 2000; Coker & Shumaker, 2003; Cosway et al., 2001; Crooks, Buckwalter, & Petitti, 2003; Dey, Misra, Desai, Mahaptra, & Padma, 1997; Elias et al., 1997; Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Grodstein, Chen, Wilson, & Manson, 2001; Gregg, Yaffe, Cauley, Polka, Blackwell, Narayan, & Cummings, 2000; Kilander, Nyman, Boberg & Lithell, 1997; Mogi, Umegaki, Hattori, Maeda, Miura, Kuzuya, Shimokata, Ando, Ito, & Igachi, 2004; Nilsson, Fastbom, & Wahlin, 2002; Ott, Stolk, van Harskamp, Pols, Hofman, & Breteler, 1999; van Boxtel, Buntinx, Houx, Mesemakers, Knowttneurus, & Jolles, 1998; Wahlin et al., 2002; Wu, Haan, Liang, Ghosh, Gonzalez, & Herman, 2003), while a minority of research findings have not observed this reduction in performance as a function of Type II diabetes (Heitner & Dickson, 1997; Lindemen, Romero, LaRue, Yau, Schale, Koehler, Baumgartner, & Garry, 2001; Scott, Kritz-Siverstein, Barrett-Connor, & Wiederholt, 1998).

Recently, Awad, Gagnon, and Messier (2004) sought to determine the effects of diabetes and IGT on neuropsychological performance. They reviewed the findings of 25 cross-sectional and 15 population-based studies and the data were interpreted according to the various study designs (e.g., population-based or cross-sectional). They also took into account the various measures of methodological control employed by each study for potentially confounding factors (e.g., age, depressive symptomatology, cardiovascular disease). Please see Table 1 in the Appendix (reproduced with the authors' permission) that displays the studies reviewed and their methodological properties.

The findings of Awad et al. (2004) were summarized according to specific neuropsychological tests and general cognitive functions using effect sizes and statistical significance. Lezak's (Lezak, 1995) classification of cognitive abilities was utilized to

accomplish this task and therefore, measures of verbal memory, non-verbal or visuospatial memory, attention, visuospatial performance, processing speed, frontal lobe/executive functions, and cognitive screening were included. Table 2 in the Appendix (reproduced with the author's permission) displays the results of the cross-sectional and population studies reviewed. Studies that were better designed and well-controlled were given more weight in their analyses.

In terms of the cross-sectional studies, non-contextual verbal memory (e.g., word list recall), processing speed, and brief cognitive screening measures were most consistently affected by Type II diabetes. Measures of non-verbal memory and executive functions were less consistently affected, with some studies reporting significant differences (between Type II diabetics and control participants) and medium to large effect sizes. Lastly, very few significant differences or medium to large effect sizes were reported for measures of visuospatial processing and auditory or visual attention. In terms of population studies, it was noted that that Type II diabetics were more likely to show poor performance on brief cognitive measures compared to controls with other measures less likely to show significant differences.

Awad et al. (2004) concluded that even among well-controlled studies, the research findings from cross-sectional and population studies are generally inconsistent. Nonetheless, the measures that appear to be most sensitive to deficits in Type II diabetes include non-contextual verbal memory, processing speed/reaction time, and brief cognitive measures (e.g., Mini Mental Status Examination (MMSE)) with measures of visuospatial functioning, auditory attention, and visual attention less likely to show significant differences between Type II diabetics and controls. Measures of executive

function and non-verbal memory have demonstrated inconsistent findings with respect to significant differences between Type II diabetics and controls.

Stewart and Liolitsa (1999) have suggested that due to the number of methodological differences between studies and the methodological weaknesses in some of the studies examining cognitive functioning in Type II diabetes including differences in sample size and composition, differential selection of neuropsychological tests and measures with varying sensitivities, and frequently not taking into account educational level, premorbid cognitive ability, other disorders commonly associated with diabetes (e.g, depression, cardiovascular disease, cerebrovascular disease), and other potential mediating factors (e.g., alcohol intake, use of centrally-acting medications), this could potentially explain the variability in the findings.

Awad et al. (2004) have also noted that a treatment confound may also contribute to the variability in findings. Specifically, the varying levels of glucoregulatory control among participants across studies may contribute to the lack of a specific pattern of dysfunction in terms of the cognitive domains affected in Type II diabetes, as will be discussed further in the introduction.

Additionally, Ryan and Geckle (2000) have suggested that the effect of Type II diabetes on cognitive functioning is greater in older people with worse glucoregulatory control. Thus, age is another important factor to consider. In concert with this, Awad et al. (2004) found that in their analysis of cross-sectional studies, the largest effect sizes were observed in studies where participants were older (mean age = 65 vs. 59 for studies that found smaller effects sizes) and had worse glucose regulation.

In summary, there appears to be a great deal of cross-sectional and population-based research that demonstrates that Type II diabetes is a risk factor for cognitive impairment in the elderly population. Additionally, this risk appears to be independent of the one associated with cerebrovascular disease, cardiovascular disease, and depression. While the specific pattern of dysfunction is currently unclear, the most consistent deficits have been observed on tasks of verbal memory, processing speed, and brief cognitive screening measures, whereas tasks that tap executive function, non-verbal memory, visuospatial functions, and basic attentional processes appear to be less commonly affected.

Type II Diabetes and Dementia

In addition to the observation of various cognitive deficits in Type II diabetes, several cross-sectional (Lindsay, Hebert, & Rockwood, 1997; Ott, Stolk, Hofman, van Harskamp, Grobbee, & Breteler, 1996) and longitudinal, prospective studies (Haan, Mungas, Gonzalez, Ortiz, Acharya, & Jagust, 2003; Knopman, Boland, Mosley, Howard, Liao, Szklo, McGovern, & Folsom, 2001; Leibson, Rocca, Hanson, Cha, Kokman, O'Brien, & Palumbo, 1997; MacKnight, Rockwood, Awalt, & McDowell, 2002; Ott et al., 1999) have examined the relationship between Type II diabetes and dementia and have observed an increased risk of cognitive decline and clinically ascertained dementia among Type II diabetics.

A recent prospective, longitudinal, population-based study examined the relationship between Type II diabetes and cognitive decline over a 6-year period in a sample of 9679 older women (Gregg et al., 2000). Compared with non-diabetic women (n=8997; mean age 72), women with Type II diabetes (n=682; mean age 72) had less

education, higher depression, a greater frequency of hypertension, and were more likely to report cardiovascular disease and stroke. Participants were tested on Digit Symbol-Coding, the Trail Making Test- Part B (TMT-B), and a modified version of the MMSE. After controlling for age, education, depression, visual impairment, heart disease, and hypertension, it was found that diabetics performed more poorly on all three tests at baseline and on the Digit Symbol-Coding and the TMT-B at follow-up 6 years later. Type II diabetics also evidenced greater cognitive decline, as defined by a change into the worst 10^{th} percentile of scores on both Digit Symbol-Coding and the TMT-B. Thus, there was a two-fold increased risk of cognitive impairment and a 74% increased risk of cognitive decline associated with Type II diabetes. The authors concluded that women with Type II diabetes have poorer cognitive functioning and a more rapid cognitive decline than non-diabetic women. Additionally, they determined that their findings could not be explained by the presence of cardiovascular disease, hypertension, overt stroke, or depression.

As part of a larger study on vascular aging conducted in France (Epidemiology of Vascular Aging Study), Fontbonne et al. (2001) examined cognitive functioning over time as a function of diabetes in a sample of elderly men and women (mean age 65) with no evidence of cognitive impairment at baseline. Of 961 participants, 55 had Type II diabetes, 103 had impaired fasting glucose (IFG), and 768 had normal fasting glucose (NFG). Compared with those with NFG, diabetics and those with IFG had more cardiovascular risk factors. At baseline, all participants performed similarly on measures of cognition (i.e., the MMSE and 8 domain-specific tests assessing visual and auditory attention, immediate verbal memory, visuospatial processing, psychomotor speed, and

logical reasoning). At the 4-year follow up, Type II diabetics tended to perform worse than those with IFG and NFG on all 8 domain-specific tests with differences reaching significance for 4 (TMT-B, Auditory Verbal Learning Test, Test of Facial Recognition, and Digit Symbol Substitution) of these measures. After adjustment for age, sex, education, hypertension, medication, and baseline scores, diabetic patients had more than a two-fold probability of cognitive decline on these 4 tests (i.e., scores declining into the worst 15% of the sample's distribution of score differences for each test) compared with the normal group. The authors concluded that Type II diabetes is associated with greater cognitive decline over time.

These findings have been substantiated by studies that have shown that in patients with multi-infarct dementia, the prevalence of diabetes is higher than in the general population (Landin, Blennow, Wallin, & Gottfries, 1993; Mortel, Wood, Pavol, Meyer, & Rexer, 1993) and that individuals who have suffered from a stroke are at greater risk of subsequent vascular dementia if they have concurrent diabetes (Tatemichi, Desmond, Paik, Figueroa, Gropen, Stern, Sano, Remien, Williams, & Mohr, 1993). Several prospective population-based studies have also shown that Type II diabetes is associated with an increased risk of vascular dementia (Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; Ott et al., 1999; Peila, Rodriguez, & Launer, 2002; Yoshitake, Kiyohara, Kato, Ohmura, Iwanmoto, Nakayama, Ohmori, Nomiyana, Kawano, Ueda, Sueshi, Tsuneyoshi, & Fujishima, 1995).

The relationship between Type II diabetes and Alzheimer's disease (AD) is less clear and previous cross-sectional case-control studies have reported relatively low rates of Type II diabetes in patients with AD (Landin et al., 1993; Mortel et al., 1993; Nielson,

Nolan, Berchtold, Sandman, Mulnard, & Cotman, 1996). However, several population-based prevalence studies have detected a positive association between Type II diabetes and AD (Kuusisto, Koivisto, Mykkanen, Helkala, Vanhanen, Hanninen, Kervinen, Kesaniemi, Riekkinen, & Laakso, 1997; Ott et al., 1996) and several cross-sectional studies have reported that individuals with AD exhibit impaired glucose regulation compared with age-matched controls (Craft, Dagogo-Jack, Wiethop, Murphy, Nevins, Fleischman, Rice, Newcomer, & Cryer, 1993; Meneilly & Hill, 1993). One cohort study observed an increased incidence of AD in Type II diabetic patients (Leibson et al., 1997) and several prospective population-based studies observed an increased risk of AD in Type II diabetics (Luchsinger et al., 2001; Ott et al., 1999; Peila et al., 2002; Yoshitake et al., 1995).

Ott et al. (1999) conducted a population study in order to determine the relationship between Type II diabetes and the risk of dementia and AD. This study was a follow-up study utilizing data from the Rotterdam study (i.e., Ott et al., 1996), a community-based cross-sectional study designed to investigate chronic disorders of the elderly. Of the 6370 that were assessed for diabetes at baseline, 692 were diagnosed with Type II diabetes. Non-demented individuals were followed up on average, 2.1 years later. After adjusting for age and gender, it was determined that diabetes almost doubled the risk of dementia (relative risk (RR): 1.9; CI: 1.3-2.8) and AD (RR: 1.9; CI: 1.2-3.1) with risks being similar for both men (RR: 1.8) and women (RR: 1.9). The relative risk for developing AD associated with Type II diabetes was 1.9 for all AD patients, 1.8 for AD participants without cerebrovascular disease, and 3.0 for AD participants with concomitant cerebrovascular disease. The relative risk for developing vascular dementia

associated with Type II diabetes was 2.0. Thus, the fraction of incident dementia attributable to Type II diabetes was 8.8% (8.1% in men and 9.2% in women). The results from this study suggest that the relative risk for dementia associated with Type II diabetes was similar in both men and women and that risk was also related to the type of treatment for Type II diabetes, with those receiving no treatment having the lowest risk and those receiving insulin having the highest risk. Although a higher risk for AD associated with Type II diabetes was seen in the presence of cerebrovascular disease, significant risk was also observed in its absence, and adjustment for other vascular risk factors and indices of cardiovascular disease made little difference to the association.

Recently, MacKnight et al. (2002) investigated the relationship between diabetes and incident dementia (vascular and AD) in a 5-year prospective longitudinal study. The data reported in this study represent phase 2 of a larger cohort study of dementia in older Canadians, the Canadian Study of Health and Aging (CSHA). A sample of 5574 (mean age 74) participants with no evidence of cognitive impairment at baseline (i.e., phase 1 of the CSHA conducted in 1991-1992) participated at the 5-year follow-up. Of the 5574 participants, 503 had a diagnosis of diabetes. The type of diabetes was not specified, but given that the study aimed to examine cognitive status in elderly individuals, it can be assumed that the majority of diabetics had Type II diabetes. Of the 5574 participants, 467 were diagnosed with incident dementia (267 with AD, 89 with vascular dementia, 63 with mixed dementia, 48 with other type dementia, and 128 with incident vascular cognitive impairment no dementia (CIND)). Diabetes was found to be associated with vascular dementia (RR: 2.03; 95% CI: 1.15-3.57), incident vascular cognitive impairment (RR: 1.62, 95% CI: 1.12-2.33), and vascular CIND (RR: 1.68, 95% CI: 1.01-2.78).

Diabetes was not associated with mixed AD/vascular dementia (RR: 0.87; 9%% CI: 0.34-2.21), or incident AD (RR: 1.30; 95% CI: 0.83-2.03). Thus, while diabetes was not found to be associated with AD, a significant association was found with incident vascular cognitive impairment including vascular dementia and vascular CIND. These results are in agreement with the cross-sectional study of the inception cohort for the CSHA where diabetes was found to be associated with vascular dementia (Rockwood, Ebly, Hachinski, & Hogan, 1997), but not with AD (Hogan, Ebly, & Rockwood, 1997).

Thus, although there are some discrepant findings (e.g., Heitner & Dickson, 1997), several prospective and cross-sectional studies suggest that Type II diabetes is associated with an increased risk of dementia. Although there is some contention in the literature as to whether Type II diabetes contributes to cognitive impairment in AD or vascular dementia or both, the most robust population-based prospective studies indicate that there is an increased risk of both subtypes of dementia in diabetic subjects. MacKnight et al. (2002) suggest that the differences observed between the studies can be explained by differences in methods utilized for diabetes diagnosis, the criteria used for diagnosis of vascular dementia and AD, and the variables chosen for inclusion in multivariate models.

Impaired Glucose Tolerance and Cognitive Impairment

Type II diabetes appears to be a major risk factor for cognitive impairment and dementia. Poor glucose regulation in non-diabetics has also been shown to be associated with cognitive decrements. Specifically, research has examined the impact of poor glucose regulation in older participants with no overt signs of Type II diabetes, but who tend to have a higher blood glucose levels in response to glucose load. Several cross-

sectional studies and population-based studies have observed that non-diabetic individuals with IGT have cognitive impairments (Convit, Wolf, Tarshish, & de Leon, 2003; Hiltunen, Keinanen-Kiukaannieimi, & Laara, 2001; Kalmijn et al., 1995; Kaplan et al., 2000; Vanhanen et al., 1998; Vanhanen, Koivisto, Karjalainen, Helkala, Laasko, Soininen, & Riekkinen, 1997).

IGT is associated with higher mortality (Balkau, Eschwege, Papoz, Richard, Claude, Warnet, & Ducimetiere, 1993) and an increased risk for cardiovascular disease (Pyorala, Laasko, & Uusitupa, 1987). Moreover, IGT is characterized by elevated insulin levels (Lillioja, Mott, Howard, Bennett, Yki-Jarvinen, Freymond, Nyomba, Zurlo, Swinburn, & Bogardus, 1988; Modan, Halkin, Almog, Lusky, Eshkol, Shefi, Shitrit, & Fuchs, 1985; Mykkanen, Kuusisto, Pyorala, & Laakso, 1993), which have been shown to be directly related to cognitive impairment (Kalmijn et al., 1995; Kuusisto et al., 1993; Kuusisto et al., 1997). Hyperinsulinemia is also associated with atherosclerosis, thrombosis, and abnormal hemodynamic processes (Defronzo, 1992; Feskens & Kromhout, 1992; Juhan-Vague, Thompson, & Jespersen, 1993; Reaven, 1988) that may potentially lead to lacunar infarcts and white matter changes and thus, impaired cognitive function (Erkiinjuntti & Hachinski, 1993).

The relationship between diabetes, IGT, and hyperinsulinemia to cognitive functions was examined in a cross-sectional study of 462 elderly men (aged 69-80; mean age 75) (Kalmijn et al., 1995) using data from the Zutphen Elderly Study (Feskens & Kromhout, 1992). Additionally, they assessed the role of cardiovascular disease and risk factors associated with insulin resistance that may potentially mediate this relationship. Compared with normoglycemic non-diabetic subjects (n=340), individuals with diabetes

(n=75), individuals with IGT (n=47), and individuals with the highest insulin levels (n=97) evidenced a greater number of errors on the MMSE after adjustment for age, occupation, smoking, cardiovascular disease (i.e., stroke, transient ischemic attack, myocardial infarction, angina pectoris, and intermittent claudication), and insulin resistance syndrome risk factors (i.e., BMI, hypertension, HDL, triglycerides, and fibrinogen). Similarly, IGT and hyperinsulinemia were found to be independently related to decreased cognitive function as assessed by the MMSE. Participants with IGT were older, had higher insulin area under the curve values, higher stroke prevalence, and had the highest prevalence of poor cognitive functioning. The findings point to a possible interaction between age, insulin and cognitive dysfunction and suggest that impairment was greater in the older (>75) rather than the younger (<75) age group. Among diabetic patients, cognitive functioning decreased with increasing concentrations of fasting plasma glucose, which is an index of short-term glycemic control. Thus, poorer glycemic control was related to poorer cognitive function in Type II diabetics. The authors concluded that IGT and hyperinsulinemia in non-diabetic individuals and Type II diabetes are all associated with cognitive impairment.

Vanhanen et al. (1997) studied cognitive functioning in Type II diabetics (n=35) and normoglycemic elderly subjects (n=73) at different risk levels for developing Type II diabetes. The risk for developing Type II diabetes was considered high if both 2-hour glucose and insulin values on an oral glucose tolerance test were higher than the median in normoglycemic subjects, and low if these values were lower than the median. Type II diabetics treated with insulin and individuals evidencing confounding factors that could potentially affect brain function (e.g., dementia, depression, stroke) were excluded.

There were no differences with respect to cardiovascular disease, hypertension, and current blood pressure between the risk groups; although Type II diabetics had a greater prevalence of hypertension than the other two groups. The increased risk group and Type II diabetics had higher 2-hour insulin levels and insulin area under the curve values than the low risk group. Compared to the low risk group (n=26; mean age 63), the high risk group (n=22; mean age 65) showed impairment on 7 (of 14) tasks measuring immediate and delayed verbal and visual memory, attention, visuomotor speed and verbal fluency after controlling for age, sex, and education. The increased risk group did not differ from the group with Type II diabetes (n=35; mean age 67) on any cognitive measures. The authors concluded that cognitive impairment was associated with an increased risk for Type II diabetes, namely, IGT and hyperinsulinemia.

Vanhanen et al. (1998) examined cognitive performance in a sample of elderly participants with persistent normal glucose tolerance (n=506; mean age 73) and persistent IGT (n=80; mean age 73). This was a follow-up study of prior research examining risk factors for atherosclerotic vascular disease in the elderly (Myykanen, Laasko, Uusitupa, & Pyorala, 1990). Glucose regulation was measured 3.5 years prior to and immediately preceding the cognitive testing. In addition to significantly increased fasting and 2-hour plasma glucose levels, individuals with IGT had significantly higher fasting and 2-hour plasma insulin levels compared to those with normal glucose tolerance. The authors observed that compared to those with normal glucose tolerance, participants with IGT scored lower on the MMSE and the long term memory scores of the Buschke Selective Reminding Test. No significant differences were observed between the two groups on the visual reproduction test, Trail Making Test or verbal fluency test. However, there

was a non-significant trend for lower scores on all cognitive measures in participants with IGT. Additionally, it was reported that age, education, and insulin levels were associated with MMSE scores in the participants with IGT. Thus, the authors concluded that persistent IGT is associated with mildly impaired cognitive functioning and that hyperinsulinemia may account for this association.

Hiltunen et al. (2001) conducted a population-based study of 379 subjects (aged 71-94) to investigate the relationship between abnormal glucose tolerance and cognitive impairment in the elderly. The sample included 65 previously diagnosed Type II diabetics, 33 previously undiagnosed Type II diabetics, 130 participants with IGT, and 151 normoglycemic subjects. The authors reported that low educational level and increasing age were the best predictors of cognitive impairment in the total study population. After adjusting for age, gender, educational level, presence of cardiovascular disease, alcohol use, number of depressive symptoms, and poor vision, abnormal glucose tolerance (including both previously undiagnosed Type II diabetes (OR:1.6; CI:0.7-4.0) and IGT (OR:1.4; CI: 0.8-2.6)) was found to be associated with impaired cognitive functioning, as assessed by the MMSE. The researchers concluded that their findings suggest that hyperglycemia and/or other associated phenomena, such as hyperinsulinemia, may lead to cognitive impairment.

The relationship between IGT and dementia has also been studied. For example, Curb, Rodriguez, Abbott, Petrovitch, Ross, Masaki, Foley, Blanchette, Harris, Chen, and White (1999) examined the relationship between diabetes and IGT and vascular dementia and AD in a historical prospective cohort study of Japanese-American men (n=3774) who were examined at ages 45 to 68 (between 1965 through 1968) and at ages 71 to 93

(between 1991 through 1993). After adjustment for age and education, the researchers found no association between diabetes and AD present either 25 or 15 years previously. However, a significant association was found between IGT and vascular dementia. The authors concluded that their findings confirmed the expected relationships between IGT and vascular dementia, but did not support an association between IGT and AD.

Recently, Convit et al. (2003) conducted a study to determine whether poor glucose tolerance was associated with deficits in memory performance and smaller hippocampal volumes in a sample of non-diabetic, non-demented middle-aged and elderly individuals (n=30; mean age 69). Decreased peripheral glucose regulation, as measured using a standardized intravenous glucose tolerance test was found to be associated with decreased general cognitive performance (as assessed by the MMSE), memory impairments (as assessed by immediate and delayed story recall), and atrophy of the hippocampus, a brain area that is key for learning and memory. The associations between IGT and memory impairments and brain atrophy were independent of age and MMSE scores. In contrast, insulin values were not related to memory, MMSE scores, or any of the brain volumes.

In sum, the research reviewed above indicates that mildly impaired glucose regulation is associated with impaired cognitive functioning in older adults with one study suggesting a link with dementia, and one study reporting an association with decreased hippocampal volumes. Several mechanisms are proposed to account for the relationship between glucose regulation and cognition.

Mechanisms by which Type II diabetes and IGT influence Cognitive Functioning

It is likely that a significant factor contributing to the apparent association between Type II diabetes, IGT, and cognitive impairment and dementia is the increased prevalence of cerebrovascular disease (Biller & Love, 1993; Mankovsky, Metzger, Molitch, & Biller, 1997) and cardiovascular risk factors (Feskens, Tuomilehto, Stengard, Pekkanen, Nissinen, & Kromhout, 1995; Stegmayr & Asplund, 1994) observed in both Type II diabetes and IGT. It is also likely that the presence of Type II diabetes or IGT with concurrent cerebrovascular disease will serve to increase the probability of or exacerbate cognitive impairment (Ryan, 2002). Nevertheless, both cross-sectional and large population-based prospective studies have demonstrated that both Type II diabetes and IGT have a detrimental effect on cognition that is independent of that associated with cerebrovascular disease (Ott et al., 1996; Ott et al., 1999; van Boxtel et al., 1998; Woo, Ho, Lau, Lau, & Yuen, 1994). Although the effects of subclinical cerebrovascular disease cannot be ruled out, the findings provide strong evidence to suggest the possibility that nonvascular, metabolic mechanisms also play a role in the pathogenesis of cognitive impairment and dementia associated with impaired glucose regulation.

Currently, what mediates the link between Type II diabetes, IGT, and cognitive dysfunction and dementia is poorly understood. Although chronic hyperglycemia and hyperinsulinemia have been considered to be the most probable candidate biological variables, researchers have not yet elucidated the underlying metabolic and hormonal pathophysiological processes that are associated with these biological variables and that are ultimately responsible for impairments in cognition (Ryan, 2002).

Hyperinsulinemia

As previously mentioned, hyperinsulinemia is characteristic of IGT and Type II diabetes, particularly in IGT and early on in the course of Type II diabetes. In addition, as part of the normal aging process, insulin levels typically rise with age (Ryan & Geckle, 2000). Thus, an increasing number of researchers have begun to explore the possibility that excessive insulin levels may independently affect the central nervous system resulting in cognitive impairments (Wickelgren, 1998). The findings thus far have indicated that hyperinsulinemia is predictive of poor performance on various cognitive measures, including verbal memory (Kalmijn et al., 1995; Kuusisto et al., 1993; Stolk, Breteler, Ott, Pols, Lamberts, Grobbee, & Hofman, 1997). Kuusisto et al. (1997) also observed an association between hyperinsulinemia and an increased risk of dementia.

How elevated insulin levels could disrupt brain functioning and negatively impact cognition is not well understood (Ryan, 2002). The way in which insulin affects brain activity has been examined and it has been discovered that insulin crosses the blood-brain barrier by way of a receptor-mediated active transport system (Baskin, Figlewicz, Woods, Porte, & Dorsa, 1987). Insulin receptors have been shown to be widely distributed throughout the brain (Hopkins & Williams, 1997; Unger & Betz, 1998) and in specific brain regions, particularly in the hypothalamus and the hippocampus, an area critical for learning and memory. Researchers have also determined that insulin modulates synaptic activity, either by inhibiting neuron firing in those brain regions or by regulating the synthesis of specific neurotransmitter reuptake transporters of dopamine and norepinephrine (for a review, see McCall & Figlewicz, 1997). Additionally, insulin has been shown to reduce choline acetyl transferase activity (Brass, Nonner, & Barrett, 1992), which could potentially lead to cognitive deficits secondary to depleted

acetylcholine levels (Stewart & Liolitsa, 1999). Impairments in the receptor-mediated active transport system appear to be associated with hyperinsulinemia and insulin resistance and may result in less insulin available to the central nervous system (Schwartz, Figlewicz, Baskin, Woods, & Porte, 1994). Despite these findings, how exactly hyperinsulinemia impairs cognitive functioning is presently unknown (Ryan, 2002).

Hyperglycemia

Hyperglycemia is the defining characteristic of Type II diabetes and IGT (Ryan, 2002) and several investigators have observed that poorer metabolic control, as indicated by different measures of hyperglycemia (e.g., glycosylated hemoglobin levels, fasting plasma glucose levels) is associated with greater cognitive impairment (Jagusch, Cramon Renner, & Hepp, 1992; Kalmijn et al., 1995; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Perlmuter, Hakimi, Hodgson-Harrington, Ginsberg, Katz, Singer, & Nathan, 1984; Reaven, Thompson, Nahum, & Haskins, 1990; Ryan, 2002). Similarly, a gradient of risk for cognitive impairment in Type II diabetes has been observed such that insulin-treated Type II diabetics have the highest risk, those treated with oral medication have a moderate risk, while those receiving no treatment (or dietary and lifestyle change recommendations) have the lowest risk (Elias et al., 1997; Ott et al., 1996).

Further evidence that supports the notion that hyperglycemia results in cognitive impairment comes from research that has evaluated glycemic control in Type II diabetes. The rationale for this research is that if cognitive dysfunction arises in Type II diabetes because of irregularities in glucose metabolism, attempts to improve glycemic control should be associated with a parallel improvement in cognition. Thus, several small

treatment intervention studies have observed that the cognitive deficits observed in Type II diabetes are reversible with improved metabolic control (Gradman, Laws, Thompson, & Reaven, 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993; Naor, Steingruber, Westhoff, Shottenfeld-Naor, & Gries, 1997). In each study, older adults with Type II diabetes completed a battery of cognitive measures before receiving an oral hypoglycemic agent, with a follow-up evaluation several months later. In addition to improved metabolic control, there was a corresponding improvement on measures of learning, memory, and attention. In particular, significant improvements were noted in the area of verbal learning and memory. These findings suggest that hyperglycemia may affect brain structures and functioning directly (Ryan, 1997).

As with hyperinsulinemia, the pathophysiological mechanisms for how hyperglycemia affects cognition are yet to be elucidated. It has been hypothesized that hyperglycemia could affect cognitive functioning in several ways. For example, it has been speculated that hyperglycemia triggers the development of advanced glycosylated end products (AGE) (Vitek, Bjattacharya, Glendening, Stopa, Vlassara, Bucala, Manogue, & Cerami, 1994) that have been shown to cause pathological damage to vascular tissues and been implicated in the development of many complications associated with Type II diabetes (Vlassara, 1997). These oxidation products have also been shown to accumulate in the hippocampus as part of the normal aging process (Li, Surini, Catsicas, Kawashima, & Bouras, 1995) and have been associated with the senile plaques and neurofibrillary tangles that are characteristic of AD. From the findings of animal and in vitro studies, it has also been speculated that hyperglycemia could also affect cognitive functioning by causing an increase in aldose reductase activity with a

corresponding accumulation of sorbitol, depletion of neural myoinositol, alterations of Na-K ATPase activity, and an increase in protein kinase C activity that could all potentially result in the disruption of nutrient and hormone transport into neurons (Porte & Schwartz, 1996).

Declines in the blood-brain barrier transport of choline, a precursor of acetylcholine has been found in Type II diabetes (Skoog, 1994). Thus, it has been hypothesized that changes in brain glucose utilization might contribute to reduced acetylcholine synthesis (Landin et al., 1993) resulting in cognitive impairment. Other neurotransmitter pathways including norepinephrine, dopamine, and serotonin have also been shown to be affected by Type II diabetes, but all of these studies have been conducted with animal models of diabetes only (McCall, 1992).

In sum, it would appear that there are a number of avenues of investigation underway in order to determine the biological underpinnings of the cognitive deficits observed in both Type II diabetes and IGT.

Glucose Ingestion and Neuropsychological Performance

It has been argued that changes in the availability of glucose (i.e., increases or decreases) to the central nervous system may alter cerebral metabolism and hence, neural activity (Korol & Gold, 1998). If deficiencies in glucose regulation exist and contribute to impairments in memory, it has been suggested that if the metabolic response can be provided exogenously (e.g., glucose is administered or injected), the memory deficit may be reduced. Therefore, the impact of glucose regulation on cognition in healthy older adults has also been examined indirectly in numerous studies that have compared cognitive performance of fasting older participants after they have ingested either a 50g

glucose solution or a saccharin solution (Allen, Gross, Aloia, & Billingsley, 1996; Craft, Murphy, & Wemstrom, 1994; Gonder-Frederick, Hall, Vogt, Cox, Green, & Gold, 1987; Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Kaplan et al., 2000; Manning, Hall, & Gold, 1990; Manning, Parsons, Cotter, & Gold, 1997; Manning, Parsons, & Gold, 1992; Manning, Stone, Korol, & Gold, 1998; Messier et al., 1997; Parsons & Gold, 1992).

In general, these studies have indicated that cognitive functioning (particularly verbal declarative memory) is facilitated by modest increases in blood glucose levels. The majority of studies that have examined the effects of exogenous glucose on cognition in healthy older adults have employed a double-blind procedure whereby participants are tested after an overnight fast on a variety of cognitive tasks after drinking a glucose or saccharin (i.e., placebo) drink. The order of beverage consumption is counterbalanced so that half the participants receive the glucose drink on the first testing session and saccharin on the second testing session, and vice versa. Thus, participants serve as their own control since they receive both the treatment and placebo. Typically, different, but comparable forms of the same cognitive tests are used in order to compare performance under the two glycemic (i.e., glucose and saccharin (or fasting)) conditions.

Hall et al. (1989) tested 11 healthy elderly adults (mean age 67) on a battery of memory tests under glucose and fasting (i.e., saccharin) conditions. They observed that glucose significantly enhanced memory on several of the subtests of the Wechsler Memory Scale including Logical Memory and the composite memory score. Additionally, they reported that participants with relatively poor glucose regulation, as determined by the peak increase in blood glucose levels from baseline (i.e., fasting)

values, were those that evidenced poorer memory performance, irrespective of glycemic condition. The authors concluded that glucose influences memory in elderly adults, but that differences in glucose regulation in individual participants may be a marker of memory impairment in the elderly, regardless of acute increases in blood glucose levels at the time of testing. These findings are in accordance with the investigations that have observed cognitive deficits in individuals with IGT and Type II diabetics, as compared to age-matched controls.

In a series of studies Manning and colleagues replicated and extended the above findings (Manning et al., 1990; Manning et al., 1992; Manning et al., 1997; Manning et al., 1998). Manning et al. (1990) sought to determine whether glucose differentially affected memory versus overall cognitive, attentional, and motor functions. They reported that in their sample of 17 elderly adults (mean age 73), performance of Logical Memory immediate (5 minutes after presentation) and delayed recall (40 minutes after presentation) of the Wechsler Memory Scale, and long term word memory of the Selective Reminding Test was significantly enhanced after glucose ingestion relative to performance on these tasks under the saccharin condition. Conversely, they found that measures of attentional, motor, and overall IQ scores were comparable under both glycemic conditions. In addition, glucose regulation was found to significantly predict performance on Logical Memory immediate and delayed recall, and long term word memory on the Selective Reminding Test such that those with relatively poor glucose regulation exhibited poor performance on these tasks on the saccharin treatment day, relative to those with better glucose regulation.

Allen et al. (1996) selected a cognitive test battery consisting mainly of non-memory tasks to administer to their sample of 28 healthy elderly adults (mean age 73). They found that performance of the delayed recall component of the Rey and Taylor Complex Figure task, a measure of non-verbal memory, was significantly better in the glucose condition compared with saccharin. In terms of non-memory measures, glucose significantly enhanced measures of verbal and figural fluency, but no significant differences between glycemic conditions were observed for other tests of executive functioning (i.e., Boston naming test, Trail Making Test – parts A and B), measures of divided attention (i.e., dichotic listening), visual discrimination (i.e., Meier visual test) or fine motor coordination (i.e., grooved pegboard). However, as has been observed in prior investigations, glucose regulation was found to influence cognitive functioning in this study. Specifically, participants with relatively poor glucose regulation were those with the poorest performance on the dichotic listening and verbal fluency tasks. In general, this study provided evidence that non-verbal memory and non-memory measures of verbal and figural fluency may be influenced by increases in peripheral glucose levels.

Given that many studies reported that the beneficial effect of glucose on memory was observed in participants who had high blood glucose levels following ingestion of glucose (i.e., those with poor glucose regulation), several studies specifically examined the interaction between glucose regulation and the memory improving effect of glucose. Messier et al. (1997) investigated the effect of glucose and peripheral glucose regulation on memory functioning in 15 healthy elderly adults. They reported that older males with worse glucose regulation had decreased performance on immediate and delayed recall of the Logical Memory subtest of the Wechsler Memory Scale and on the free recall and

recognition components of a word list task compared with those with better glucose regulation. The memory-improving effect of glucose on performance of the Logical Memory test reported in many earlier studies (Craft et al., 1994; Craft, Zallen, & Baker, 1992; Hall et al., 1989; Manning et al., 1992; Parsons & Gold, 1992) was observed in this study in those with worse glucose regulation, but did not reach significance. Glucose was also found to enhance the performance of men with worse glucose regulation on the recall portion of a word list test with no such effect apparent for better regulators. Performance on the recognition portion of this task was significantly poorer for men with worse regulation relative to men with better regulation. On the Digit Span Forward subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), glucose enhanced the performance of older women with worse glucose regulation relative to the saccharin condition, while the reverse was observed for women with better glucose regulation. In fact, the performance of women with better glucose regulation was worse than that of women with worse glucose regulation on this task after ingesting glucose. In men, worse regulators performed more poorly than better regulators on Digit Span Backward in the saccharin condition. This study provided evidence that glucose regulation influences performance on cognitive measures and replicates previous findings that exogenous glucose can have an effect on certain aspects of cognitive functioning.

Kaplan et al. (2000) recently sought to determine whether various measures of glucose regulation were associated with cognitive functioning in 20 healthy elderly individuals and to further determine the influence of glucose and other common carbohydrate foods on cognitive performance. The procedure utilized in this study was similar to previous studies in the literature with the exception that, in a counterbalanced

fashion across participants, each participant was administered the following: a saccharin (placebo) drink, glucose drink, mashed potatoes, and barley. The three treatment conditions all contained 50g of available carbohydrate, but the glucose drink and mashed potatoes had a high glycemic index (i.e., raised blood glucose levels after consumption), while the barley had a low glycemic index (i.e., did not raise blood glucose levels after consumption). The tests administered were paragraph recall, word list recall, and a visuomotor task (i.e., Trail Making Test – part B). Using homeostasis model assessment (HOMA), the authors estimated β cell function and insulin resistance as indicators of glucose regulation with lower β cell and higher insulin resistance values representing relative impairments. In addition, incremental area under the glucose response curve (gAUC) was measured as an indicator of glucose regulation with higher values representing worse regulation. In general, the authors observed that a higher gAUC, poor β cell function, low insulin resistance, and low body mass index were associated with poor baseline performance on immediate and delayed verbal declarative memory and visuomotor performance in healthy elderly individuals. Furthermore, consuming 50g of carbohydrate as glucose, potatoes or barley enhanced performance on paragraph and word list recall and the Trail Making Test – part B in individuals with poor glucose regulation. Thus, individuals with relatively poor glucose regulation were observed to perform worse on cognitive tasks than those with better regulation and appeared to be most sensitive to the effects of carbohydrate consumption.

Importantly, Greenwood et al. (2003) observed that adults with Type II diabetes with poorer glycemic control performed worse on tasks of verbal declarative memory, and that acute ingestion of high glycemic index carbohydrate foods resulted in further

decreased performance. Thus, glucose improvement of cognition appears to be limited to non-diabetic individuals.

In summary, numerous studies have observed that performance on tasks of verbal declarative memory in non-diabetic older adults appears to be sensitive to enhancement with glucose. Several studies have also shown that other cognitive functions (i.e., executive function, attention) may be sensitive to this glucose-related enhancement. Furthermore, it has been observed that glucose improvement of memory is associated with poor glucose regulation, although this may not be the case for diabetic patients.

Mechanisms by which Glucose Ingestion influences Cognitive Functioning in Healthy Older Adults

A number of different mechanisms have been proposed to account for glucose enhancement of memory. Firstly, it has been hypothesized that localized deficits in extracellular glucose in the hippocampus (due to either high neuronal glucose uptake or poor transfer of glucose to extracellular space from endothelial cells (McNay & Gold, 2001) could be alleviated by increasing blood glucose levels. Secondly, it has been suggested that because a number of neurotransmitters (as discussed above) such as acetylcholine are dependent on glucose supply for their synthesis, ingestion or injection of glucose is thought to facilitate neurotransmitter synthesis and contribute to improved memory functioning. Peripheral mechanisms have also been hypothesized. Specifically, it has been suggested that glucose acts on a mechanism in the liver, which sends a neural signal to the brain, possibly via gut peptides or the vagus nerve, that subsequently results in changes in the physiological processes that underlie memory functioning. The presence of glucose sensitive neurons (i.e., neurons that change their activity depending

on the level of glucose in extracellular space) in the brain and the periphery have also been hypothesized to be a mechanism by which glucose may enhance memory functioning (Kaplan et al., 2000; Messier, 2004).

It is important to note that there is a close correspondence between the rise of blood glucose and the rise in blood insulin following the ingestion of glucose. Few data exist about a facilitative effect of insulin, but it is nevertheless difficult to dissociate the effect of insulin from the memory-improving action of ingested or injected glucose. The observations from animal studies that show that glucose injected in the brain facilitates memory (Lee, Graham, & Gold, 1988) and therefore suggests a central action. However, other data also suggest a role of insulin. For example, two animal experiments have shown the ability of small doses of insulin (0.4-0.8 units/kg) to reverse the amnesia produced by a 2 mg/kg scopolamine injection (Blanchard & Duncan, 1997; Messier & Destrade, 1994) and that intracerebroventricular injection of insulin can facilitate memory (Park, Seeley, Craft, & Woods, 2000).

A difficulty in this area of research is that the injection of exogenous insulin can cause a decrease in blood glucose levels leading to hypoglycemia that is itself associated with impaired memory (Kopf & Baratti, 1995; 1996; Kopf, Boccia, & Baratti, 1998; Santucci, Schroeder, & Riccio, 1990). The only method of determining the impact of insulin on brain function independently of glucose levels is the euglycemic or hyperglycemic clamp. This procedure requires that participants (human or animal) be fitted with catheters allowing the sampling of blood glucose and the simultaneous infusion of glucose or hormones (such as insulin, glucagon or somatostatin) to manipulate blood glucose levels. The euglycemic clamp results in the maintenance of blood glucose

at normal fasting levels (i.e., 5-6 mmol/l) whereas the hyperglycemic clamp results in the maintenance of blood glucose at higher levels (e.g., 10-12 mmol/l).

Experiments conducted by Craft and colleagues have generally been interpreted as showing that insulin is involved in the mediation of the glucose memory improving effect. For example, Craft, Asthana, Newcomer, Wilkinson, Matos, Baker, Cherrier, Lofgreen, Latendresse, Petrova, Plymate, Raskind, Grimwood, and Veith (1999) showed that raising blood insulin levels while keeping blood glucose levels constant (using the euglycemic clamp) results in improved memory. However, in this experiment, glucose had to be continuously injected in order to keep glucose levels from falling while insulin levels were raised. Thus, this investigation would appear to have more specifically demonstrated that increased blood glucose levels are not necessary to observe memory improvement. Additionally, the results fall short of clearly demonstrating that insulin mediates the effect of glucose on memory because glucose is continuously injected during the euglycemic clamp. As a result of these difficulties, the role of insulin in cognition functioning remains unclear although it has been implicated in other brain functions (for an extensive review see Craft and Watson (2004) and Gerozissis (2003)).

Thesis Foci

The findings reviewed above provide evidence for the notion that both Type II diabetes and IGT are associated with cognitive impairment and place individuals at higher risk for cognitive decline and dementia. Additionally, the research has demonstrated that these relationships are independent of depression, cerebrovascular and cardiovascular disease, although it is likely that these conditions increase the likelihood and/or severity of deficits. It has also been demonstrated in a number of studies that

poorer glucose regulation, even in the absence of overt Type II diabetes or IGT, is associated with deficits in cognitive functioning. The areas that appear to be affected by Type II diabetes, IGT, and poor glucose regulation include verbal memory, processing speed, and performance on brief cognitive measures, and to a lesser extent, executive functioning, working memory, attention/concentration, and visuospatial memory. The research also suggests that age mediates the relationship between poor glucose regulation and neuropsychological functioning such that increasing age in combination with poor glycemic control results in the greatest risk of neuropsychological impairment. The potential mechanisms that have been hypothesized to account for this impairment suggest that both chronic hyperglycemia and hyperinsulinemia are two important underlying variables that likely contribute to the negative impact on cognition seen in Type II diabetes, IGT and poor glucose regulation. As reviewed above, many studies also suggest that glucose administered exogenously in healthy older adults may enhance cognitive performance, particularly on tasks of verbal memory, and preliminary findings indicate that this memory facilitation may be greater for those with poor glucose regulation.

The abovementioned findings in conjunction with the increased prevalence of cognitive impairments and abnormal glucose tolerance as a function of normal aging suggest that it is important to examine neuropsychological functioning in healthy older adults (i.e., without IGT or Type II diabetes) as a function of glucose regulation to determine if those with poorer glucose regulation will exhibit performance decrements on various measures. This research would converge with the findings in Type II diabetics and individuals with IGT and provide additional support for the notion of cognitive

dysfunction as a result of abnormalities in glucose regulation and associated difficulties (i.e., hyperinsulinemia). The study of the effect of varying levels of glucose regulation and their impact on cognition has been relatively neglected in healthy older adults. This research is crucial in order to clarify if impaired glucose regulation is indeed a risk factor for deficits in neuropsychological functioning and hence, to aid in the understanding of the nature of cognitive impairment observed in normal aging. It is also of interest to determine if the ingestion of glucose will facilitate performance on these measures as a function of glucose regulation, as it has been suggested that glucose improvement of memory is a hallmark of poor glucose regulation. Thus, the present study examined the effect of glucose regulation and glucose ingestion on cognitive functioning in healthy older adults.

A comprehensive set of cognitive measures was utilized in the present study. Specifically, six measures of attention, working memory, and processing speed, three measures of immediate verbal memory (one with a delayed memory component), one measure of immediate and delayed visuospatial memory, and one measure of central executive functioning were employed. The cognitive domains that have been shown to be impaired in Type II diabetes and IGT have not been consistent. Although verbal declarative memory, as assessed by paragraph recall and word-list learning tasks, and processing speed appear to be the most typically affected in previous research, other cognitive domains including attention/concentration, visuospatial memory, and executive functioning have not been shown to be consistently impaired. Thus, the present study used a number of tests that tap these cognitive areas in an effort to help elucidate the nature of cognitive deficits associated with abnormalities in glucose regulation.

In order to ensure sensitivity and specificity of the measures, seven subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997a) and the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997b) were utilized, as they have been shown to have good psychometric properties. Moreover, many of the measures have been utilized in previous research in this area allowing for comparisons of the present results with these prior studies. Additionally, the Rey and Taylor Complex Figure Task was used to assess visuospatial memory, two experimental word-list learning tasks were employed to assess verbal memory, and the Modified Brown-Peterson task was used to assess executive functioning. The measures are described in more detail in the Methods section.

In order to further aid in the understanding of the effect of glucose regulation on cognition in aging and to examine the interaction between age and glucose regulation on cognition, a sample of healthy older adults was used. Thus, men and women aged 55 and older were recruited to participate in the present study. The definition of an older person is somewhat difficult. The age at which late adulthood (Weiten & Lloyd, 1997) or "old age" (Cavanaugh, 1993) begins has typically been identified as 65 although this is an arbitrary boundary. Some studies have included participants in their 50s, while other investigations classify people as "older" at age 60 or 65 (Lindley, 1989 as cited in Lezak, 1995). However, several reports indicate (based on pooled normative data for standard clinical memory tests) that a significant percentage (41%) of individuals begin to evidence age-associated deficits in memory functioning in the fifth decade of life and that the prevalence of age-associated deficits in memory functioning increases as individuals age (Blackburn & La Rue, 1989; Crook, Bartus, Ferris, Whitehouse, Cohen, & Gershon,

1986; Small, La Rue, Komo, Kaplan, & Mandelkern, 1995). Similarly, both physiological and cognitive changes rapidly begin to take place within the age range of 50 to 65 (Lezak, 1995). Therefore, in selecting age 55 as the cut-off for participants and recruiting individuals 55 and older, the present research sought to capitalize on the well-documented memory deficits in this population in order to increase the probability of observing cognitive impairments and facilitation of memory by glucose.

Several biological indices were measured for the determination of glucose regulation. Specifically, fasting blood glucose and insulin levels were measured in addition to measures of glucose 30, 60 and 120 minutes after ingestion of a glucose drink, and measures of insulin 60 and 120 minutes after ingestion of the glucose drink. These indices are accepted means of evaluating glucose regulation and insulin tolerance in individuals. Additionally, cholesterol, triglycerides and c-peptide were measured because of their association with impaired glucose regulation and as they are risk factors for cerebrovascular disease and hence, cognitive dysfunction (Desmond, Tatemichi, Paik, & Stern, 1993; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch et al., 1992; Kilander et al., 1997; Vanhanen et al., 1998; Vanhanen, Kuusisto, Koivisto, Mykkanen, Helkala, Hanninen, Riekkinen, Soininen, & Laakso, 1999). They were measured to determine their potential effects on cognitive dysfunction. The measurement of these biological indices is described in the Methods section.

Given previous research suggesting that cerebrovascular disease, cardiovascular risk factors, depression, and other conditions (to be discussed in the Participants section) affect cognitive functioning either directly or in conjunction with abnormal glucose tolerance, individuals recruited with these conditions were excluded from participating in

the study to ensure that the present results were not confounded. A more detailed explanation of the conditions for exclusion from the study and/or exclusion from the analyses is given in the Methods section.

Hypotheses

Hypothesis 1

As previous research has noted that poor glucose regulation is associated with greater cognitive decrements, it is hypothesized that progressively worse glucose regulation will result in progressively worse performance on all neuropsychological measures.

Hypothesis 2

As it has been well-documented in prior research that cognition generally declines with age, it is hypothesized that increasing age will result in worse performance on all neuropsychological measures.

Hypothesis 3

As per recent findings (Awad et al., 2004; Ryan & Geckle, 2002), it is hypothesized that poor glucose regulation and increasing age will interact to produce the greatest performance decrements on all neuropsychological measures.

Hypothesis 4

Lastly, it is hypothesized that performance on the neuropsychological measures will differ as a function of solution ingested. Specifically, as per the research demonstration the cognition-improving effect of glucose, performance on cognitive tasks will be better in the glucose condition relative to the saccharin condition. Additionally, this effect will be more prominent in participants with worse glucose regulation.

METHOD

Participants

Recruitment. A total of 158 individuals volunteered to participate in this study. Healthy older male and female volunteers were consecutively recruited from the community through local newspaper and newsletter advertisements, presentations at local seniors' community resource centers and events, and fitness classes for individuals 55 and older. Interested participants phoned the Memory Lab at the University of Ottawa, as indicated on the advertisements. Those that learned about the study through presentations had the opportunity to write their name and telephone number on a sign-up sheet and were informed that they would be contacted to further discuss the study and to determine if they were eligible to participate on the basis of established criteria. Volunteers were initially screened with a telephone questionnaire and 57 were excluded from participating on the basis of these criteria (see Screening below). Eight participants met the initial screening criteria, but were subsequently excluded from statistical analyses as a result of not completing all three visits (see Procedure below). Thus, the predictive ability of glucose regulation with respect to cognitive performance was evaluated in 93 healthy male (n=19) and female (n=74) older participants who ranged in age from 55 to 88 (M = 70.05, S.E.M. = 8.28).

Screening. Interested participants were contacted by telephone in order to potentially schedule the first of three sessions (see Procedure for description of sessions) if they met the criteria established for participation in the study. A short rationale for the study and a description of the three sessions was provided for all potential participants and they were also informed that their participation in the study was voluntary and that all

information gathered from them would remain confidential. Any potential questions or concerns regarding the study were addressed. Interested potential participants were screened with a telephone questionnaire and were informed that in the event that they could not be included in the study, their answers would be immediately destroyed. Their age and medication regimen was also obtained. Potential participants were excluded from the study on the basis of the following criteria: self-reported hypoglycemia, diabetes (Type I or Type II), hepatitis B, current alcohol or drug abuse, current depression, any neurological disorder (including cerebral hemorrhage, strokes, tumors, transient ischemic attack, or lesions), head injury (throughout lifetime) with a loss of consciousness, self-reported memory problems, loss of consciousness for more than 1 hour, and current consultation with a psychiatrist. Participants were excluded from participating from the study on the basis of these criteria because these factors may have potentially confounded the measures of glucose regulation and/or performance on the cognitive tasks. Alcohol abuse was operationally defined as the consumption of more than 54g of ethanol per day (i.e., equivalent to 4 drinks containing an average of 13.6g of ethanol) for a period exceeding one month (Skinner, 1982; Skinner & Allen, 1982) during the past two months. Participants were screened for depressive symptomatology in the first session with the Beck Depression Inventory (BDI; Beck, 1987), as will be described in the Procedure. Those with scores above the minimal range (greater than 9) were excluded from the statistical analyses. Participants were also screened for dementia with the MMSE (Folstein, Folstein, & McHugh, 1975) during the first session (as will be described in the Procedure) and those with a score of less than 24 out of 30 were excluded from statistical analyses as this factor (possible dementia) may have potentially

confounded performance on the cognitive tasks. For participants who met the criteria for the study, the first session was scheduled. Participants were paid $20.00 for their participation at the end of the study. The present research received ethics approval from the Human Ethics Committee of the School of Psychology at the University of Ottawa (see Appendix).

Procedure

This study involved three morning visits to the Memory Laboratory at the University of Ottawa and participants were fasting (with the exception of water) since midnight on the night before each visit. This fasting protocol is similar to what has been carried out in previous studies that have demonstrated both hyperglycemic facilitation and differences in performance as a function of glucose regulation (Craft et al., 1994; Messier et al., 1999). Participants were seen individually for each visit. One doctoral student in clinical psychology conducted the screening interviews and the three sessions (including the test administration), and was trained by a registered clinical neuropsychologist in the administration of the tests and the screening interview.

First Session. This first session was scheduled between 8 and 9 in the morning in order to minimize potential confounds associated with the time of testing, and lasted approximately 2.5 hours. The first part (i.e., 30 minutes) of the session was conducted in the memory laboratory in a quiet testing room at the University of Ottawa. Upon arrival to the memory laboratory, participants read and completed the informed consent form. They kept a copy of this form so that they would have the details of the study in writing so as to ensure adherence to the research protocol. Participants also had the opportunity to have their questions and/or concerns addressed and any details of their involvement in

the study explained. Participants had their weight and height measured and detailed information was obtained on the type and average frequency of weekly exercise in which they engaged. Their education level (i.e., number of years full-time) was obtained. One year of part-time education was considered 0.5 years of full-time education. They also completed the BDI-II (Beck, 1987) and the MMSE (Folstein et al., 1975). Participants who obtained a score below 24 (out of 30) on the MMSE (Folstein et al., 1975) and/or a score above the minimal range (a score of 16 or above) on the BDI (Beck, 1987) were excluded from the statistical analyses. Participants were asked if they had complied with the instructions to fast after midnight (with the exception of water) and if so, they were accompanied to the University of Ottawa's Health Center Laboratory for a glucose tolerance test.

A nurse took blood samples from each participant via venous puncture. These blood samples were obtained for the determination of glucose regulation and several other biological indices. Fasting blood glucose and insulin levels were measured prior to ingesting a 75g glucose solution (296ml) and glucose levels were measured again 30, 60, and 120 minutes post ingestion. Cholesterol (HDL, LDL, and total), c-peptide, and triglycerides were measured prior to ingesting the 75g glucose drink. All blood sample tests were conducted by DynaCare laboratories, which normally process all tests conducted at the University of Ottawa Health Centre. The fasting blood sample was obtained to determine fasting glucose levels (Glucose oxidase-Roche Modular Glucose method using Vitros 750 XRC Series apparatus), insulin (most samples measured using Chemiluminescent Immunoassay using DPC-Immunlite or Roche Elecsys 2010 and others, using a radioimmunoassay method using DPC Coat-A-Count), c-peptide (most

samples measured using Chemiluminescent Immunoassay using DPC-Immunlite and others using a radioimmunoassay method using EURO/DPC's Double Antibody C-Peptide), total cholesterol (Enzymatic without extraction; Roche Modular method using Vitros 750 XRC Series apparatus), LDL cholesterol (Calculation: LDL = Total cholesterol – HDL cholesterol – (Triglycerides/2.2)), HDL cholesterol (Enzymatic Colorimetric; Roche Modular method using Vitros 750 XRC Series apparatus), total triglycerides (Enzymatic Colorimetric; Roche Modular method using Vitros 750 XRC Series apparatus) and total cholesterol/HDL cholesterol ratio levels. Blood test results were also sent to Dr. Bruyère, a specialist in internal medicine at the Royal Ottawa Hospital for clinical interpretation. Specifically, if a participants' glucose values fell within the range indicative of Type II diabetes as established by the American Diabetes Association (1990), that individual would be contacted and counseled to seek further evaluation, and would subsequently be excluded from the statistical analyses. No participants were excluded from the analyses on the basis of this criterion.

Using the glucose and insulin values obtained from the blood samples during the oral glucose tolerance test, several glucoregulatory indices were derived and evaluated. These glucoregulatory indices can be separated into three categories. The first category is evoked responses, which consist of estimates of the increase of blood glucose or insulin from fasting levels. Of these estimates, the area under the curve of evoked glucose levels (AUCg) is the only one that takes into account all 4 measurements of blood glucose. A high evoked glucose response is generally the result of poor insulin secretion and/or poor sensitivity of tissues to the action of insulin. A high evoked insulin response, which may or may not be associated with high blood glucose levels, usually reflects insulin

resistance (poor sensitivity of the tissues to the action of insulin). In the early stages of insulin resistance, compensatory increases in insulin levels are observed and manage to control blood glucose levels toward normal values. As insulin sensitivity decreases further, fasting and evoked blood glucose are markedly elevated and reflect the failure of the pancreas to secrete sufficient insulin to compensate for insulin resistance.

The second category of indices comprises recovery measures that are estimates of the speed at which glucose is cleared from the bloodstream or, in the case of insulin, how fast insulin levels return towards baseline levels. Two other indices (beta-cell function and insulin resistance) were derived from the basal homeostatic model assessment of glucoregulation (HOMA) (Hosker, Matthews, Rudenski, Burnett, Darling, Brown, & Turner, 1985; Matthews, Hosker, Rudenski, Naylor, Treacher, & Turner, 1985). This model uses fasting insulin and glucose levels to calculate an estimate of beta cell function (expressed as a percentage of the estimate for 35-year old (or younger) normal weight participants) and insulin resistance.

Second session. This second session was conducted approximately one week after the first session to ensure that all participants received a comparable testing procedure. It was conducted in the same testing room used for the first session. It was scheduled between 8 and 10 in the morning and lasted approximately 1 hour and 45 minutes. Upon arrival to the memory laboratory, fasting blood glucose levels were measured to verify compliance with the instructions to fast. A Glucolet lancet Elite Glucometer (Bayer, Canada) was used to obtain a drop of blood from which blood glucose was measured with and Elite Glucometer (Bayer, Canada) (Messier & Kent, 1995). Next, participants ingested a 240ml lemon-flavoured solution (Kool Aid powder

without glucose) that was sweetened with either glucose (50g) or saccharin (50.6mg). These doses were selected as a result of previous studies that have shown an association between glucose and memory performance in older adults (Craft et al., 1994; Messier et al., 1997). Both the experimenter and participant were blind to the type of solution given, and solution type was counterbalanced such that half the participants received the glucose solution and half received the saccharin solution in the second session. The administration of solutions was determined randomly whereby each participant had an equal probability of receiving either solution first (i.e., in the second session). Following the telephone interview, each participant was assigned a number such that those assigned an even number received the glucose solution first and those assigned an odd number would receive the saccharin solution first. In order to control for the taste difference between the solutions, 4mg of saccharin was added to the glucose drink (Messier et al., 1999).

Five minutes after ingesting the 240ml solution, participants began the cognitive testing which consisted of the Arithmetic, Digit-Symbol Coding, Symbol Search, Digit Span, Spatial Span, and Letter-Number Sequencing subtests from the WAIS-III and WMS-III, a modified administration of the Logical Memory subtest of the WMS-III the Modified Brown-Peterson task, the Rey and Taylor Complex Figure task, Verbal Free Recall, and Order Recall. The 5-minute interval between drink consumption and testing has been previously used in studies demonstrating glucose facilitation of cognitive performance (Messier et al., 1997; Messier et al., 1999). Blood glucose levels were measured 60 minutes following ingestion of the solution. As a precautionary measure, if a participant's blood glucose level reached 2.5 mmol/L or less or if the participant

reported weakness or dizziness, he or she was given a 100ml solution containing 20% glucose to raise their blood glucose level. Their blood glucose level was monitored until a normal level had been achieved and this participant was then excluded from the study. One participant was excluded on this basis. A detailed description of the tests administered in the present study will follow (see Measures).

After the 5-minute interval had elapsed, participants completed the cognitive tests in the following order: Arithmetic, Digit-Symbol Coding, Modified-Brown Peterson task, Symbol Search, Digit Span, Spatial Span, Logical Memory immediate recall, Rey or Taylor Complex Figure Task copy, Rey or Taylor Complex Figure Task immediate recall, Verbal Free Recall, Logical Memory delayed recall, Rey or Taylor Complex Figure Task delayed recall, Letter-Number Sequencing, and Order Recall. Please see Appendix for study protocol and tests administered.

Third Session. This session was conducted approximately one week after the second session to ensure that all participants received a comparable testing procedure. The procedure for the third session was identical to the second with two exceptions. First, participants ingested the alternate solution (i.e., saccharin if they received glucose in the first session and glucose if they received saccharin in the first session). Secondly, participants were administered alternate forms of Logical Memory (i.e., Story A if they heard Story B in the second session, and vice versa), the Complex Figure Task (i.e., Rey Complex Figure if they completed the Taylor Complex Figure in the second session, and vice versa), and the Arithmetic subtest. The other working memory and processing speed measures (i.e., Digit-Symbol Coding, Symbol Search, Digit Span, Spatial Span, and Letter-Number Sequencing) were identical to those of the second session. Verbal Free

Recall, Order Recall, and the Modified Brown-Peterson task consisted of identical stimuli, but the stimuli were administered in alternate orders, as will be discussed in the Measures section. At the end of the testing session, participants were paid $20.00 in cash and signed for receipt of the money. In order to verify that participants were blind to the solutions ingested, they were also asked to identify the order of solutions they believed they had ingested.

Measures

Note: To simplify the presentation of the thesis, the statistical methodology is presented within the results section.

Screening Measures

BDI. The Beck Depression Inventory (BDI; Beck, 1987) is a 21-item self-report instrument that measures the severity of depression in adolescents and adults aged 13 to 80. It assesses symptoms of depression that correspond with DSM-III-R criteria. Scores of ≤ 9 = no depression, 10-18 = mild to moderate depression, 19-29 = moderate depression, and 30-63 = severe depression. It was selected because of its simplicity of administration, scoring and interpretation in addition to its associated validity and reliability.

MMSE. The Mini-Mental State Examination (MMSE; Folstein et al., 1975) was chosen because it is the most widely used cognitive screening measure and is short and easy to administer. It is a brief, objective assessment of cognitive functioning and is often used as a screening tool for dementia and as a measure of change in cognitive status (Tombaugh, McDowell, Kristjansson, & Hubley, 1996). It includes both verbal and non-verbal items. Normative and validation research have been conducted on the MMSE

across many samples of older individuals differing in age and education (Crum, Anthony, Bassett, & Folstein, 1993), language and cultural background (Mungas, Marshall, Weldon, Haan, & Reed, 1996), and medical-neuropsychiatric diagnoses (Folstein et al., 1975). In their review of the MMSE, Tombaugh and McIntyre (1992) concluded that the MMSE possessed moderate to high reliability coefficients. In a sample of 406 healthy older adults, a low reliability coefficient was reported ($\alpha = .62$). In older adults with Alzheimer's disease (n=119), a higher coefficient was reported ($\alpha = .81$) (Tombaugh et al., 1996). Test-retest reliability of the MMSE has ranged from $r = .55$ (Schmand, Linderboom, Jaap, Launer, Lenore, Dinkgreve, & Marc, 1995) to $r = .93$ (Stuss, Meiran, Guzman, Lafleche, & Willmer, 1996).

Cognitive Measures

Seven of the eleven measures were taken from the WAIS-III and WMS-III. These measures were selected on the basis of their reliability and validity. Furthermore, the WAIS-III and WMS-III were both normed on excellent standardization samples of 2,450 and 1,250 individuals, respectively, in the United States (aged 16-89) stratified according to age, race-ethnicity, education, and geographic region (Wechsler, 1997c). The remaining three measures were experimental tasks designed to measure verbal list learning and memory, and executive functioning.

Measures of attentional processes and working memory:

Simple and complex attentional processes were assessed using the subtests that comprise the Working Memory (i.e., Arithmetic, Digit Span, and Letter-Number Sequencing) and Processing Speed (i.e., Digit-Symbol Coding and Symbol Search) indices of the WAIS-III (Wechsler, 1997a), and the Spatial Span subtest WMS-III

(Wechsler, 1997b). The Working Memory Index (WMI) provides information regarding an individual's ability to attend to verbally presented information, to process information in memory and then to formulate a response. The Processing Speed Index (PSI) provides a measure of an individual's ability to process simple or routine visual information quickly and efficiently and to rapidly perform tasks based on that information. All six subtests were administered according to the standard administration of the WAIS-III (Wechsler, 1997a) and the WMS-III (Wechsler, 1997b).

Arithmetic. Participants were orally presented with arithmetic problems and were required to solve them without written aids and produce the correct answers orally within the time limit indicated for each item. Items 1 to 18 resulted in 1 point for each correct answer within the time limit, while items 19 and 20 resulted in 1 or 2 points stratified in this manner to award an additional point for a correct answer in very short amount of time (i.e., 2 points for a correct answer in 1 to 10 sec. and 1 point for 11 to 120 sec.). If a participant received a score of 0 on 4 consecutive items before arriving at item 16, the subtest was discontinued as per the standard administration instructions of the WAIS-III (Wechsler, 1997a). Reliability of this subtest for adults aged 55 to 89 ranges from $r = .77$ to .91. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 74 and aged 75 to 89 has been reported at $r = .88$ and .84, respectively. In terms of construct and discriminant validity, scores on Arithmetic have the strongest correlations with other WAIS-III measures of working memory (i.e., Digit Span, $r = .55$) and the weakest correlations with tasks of perceptual organization (i.e., Object Assembly, $r = .39$), and processing speed (i.e., Digit-Symbol coding, $r = .43$) (Wechsler, 1997c).

Digit Span. Digit Span consists of two tasks administered independently of each other: Digit Span Forward and Digit Span Backward. Participants were orally presented with a series of progressively longer number sequences. For Digit Span Forward, the participant was required to repeat the number sequence in the same order, as presented. For Digit Span Backward, the participant was required to repeat the number sequence in the reverse order. There are 7 items in both Digit Span Forward and Digit Span Backward with 2 trials comprising each item. Each trial (within an item) has the same amount of numbers to be recalled. One point is scored for each correct trial and thus, a maximum of two points can be awarded for any given item. If the participant failed both trials of an item, the subtest was discontinued. Reliability of this subtest for adults aged 55 to 89 ranges from r = .87 to .93. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 74 and aged 75 to 89 has been reported at r = .89 and .73, respectively. In terms of construct and discriminant validity, scaled scores on digit span have the strongest correlations with other WAIS-III measures of working memory (i.e., Letter-Number Sequencing, r = .57) and the weakest correlations with tasks of verbal comprehension (i.e., Comprehension, r = .39), perceptual organization (i.e., Block Design, r = .36), and processing speed (i.e., Digit-Symbol Coding, r = .36) (Wechsler, 1997c).

Letter-Number Sequencing. For this subtest, participants were orally presented with a combination of numbers and letters and were asked to recall the numbers first, in ascending order, and then the letters in alphabetical order. The sequences of numbers and letters become longer as the subtest progresses. There are 7 items with 3 trials, and each trial (within an item) has the same sequence length. Each trial consists of a different combination of numbers and letters. One point is scored for each correct trial and thus, a

maximum of three points can be awarded for any given item. If the participant failed all three trials of an item, the subtest was discontinued. Reliability of this subtest for adults aged 55 to 89 ranges from r = .75 to .88. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 74 and aged 75 to 89 has been reported at r = .80 and .71, respectively. In terms of construct and discriminant validity, scores on Letter-Number Sequencing have the strongest correlations with other WAIS-III measures of working memory (i.e., Digit Span, r = .57) and the weakest correlations with tasks of verbal comprehension (i.e., Comprehension, r = .44), perceptual organization (i.e., Block Design, r = .43), and processing speed (i.e., Digit-Symbol Coding, r = .44) (Wechsler, 1997c).

Spatial Span. Spatial Span consists of two tasks administered independently of each other: Spatial Span Forward and Spatial Span Backward. The examiner touched blocks in a series of progressively longer sequences that the participant observed. In Spatial Span Forward, participants were required to repeat the sequence in the same order as presented. In Spatial Span Backward, participants were required to repeat the sequence in the reverse order. There are 7 items in both Spatial Span Forward and Spatial Span Backward with 2 trials comprising each item. Each trial (within an item) has the same sequence length. One point was scored for each correct trial and thus, a maximum of two points can be awarded for any given item. If the participant failed both trials of an item, the subtest was discontinued. Reliability of this subtest for adults aged 55 to 89 ranges from r = .71 to .81. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 89 has been reported at r = .70. In terms of construct and discriminant validity, scaled scores on Spatial Span have the strongest correlations with other WMS-III measures of working memory (i..e., Letter-Number Sequencing, r = .45) and the

weakest correlations with measures of verbal (i.e., Verbal Paired Associates I , r = .20)and non-verbal memory tasks (i.e., Faces I recognition, r = .13) (Wechsler, 1997c).

Digit-Symbol Coding. For this subtest, the participant viewed an array of boxes (n=133) that had numbers in the top part and were blank in the lower part. They were required to copy the correct symbol that corresponded with the number shown by referring to a digit-symbol key at the top of the sheet. One point was scored for each correctly copied symbol drawn within the 120-second time limit. Reliability of this subtest for adults aged 55 to 89 ranges from r = .86 to .87. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 74 and aged 75 to 89 has been reported at r = .86 and .91, respectively. In terms of construct and discriminant validity, scores on Digit-Symbol Coding have the strongest correlations with other WAIS-III measures of processing speed (i.e., Symbol Search, r = .65) and the weakest correlations with tasks of verbal comprehension (i.e., Comprehension, r = .37), working memory (i.e., Digit Span, r = .36), and perceptual organization (i.e., Block Design, r = .41) (Wechsler, 1997c).

Symbol Search. For this subtest, participants were required to visually scan two groups of symbols: a target group (composed of two symbols) and a search group (composed of five symbols). They indicated whether either of the target symbols matched any of the symbols in the search group by drawing a slash in either a "yes" or "no" box. One point was scored for each correct item in the 120-second time limit. Reliability of this subtest for adults aged 55 to 89 ranges from r = .75 to .79. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 74 and aged 75 to 89 has been reported at r = .79 and .80, respectively. In terms of construct and discriminant validity, scores on Symbol Search have the strongest correlations with other WAIS-III measures

of processing speed (i.e., Digit-Symbol Coding, r = .65) and the weakest correlations with tasks of verbal comprehension (i.e., Comprehension, r = .44), working memory (i.e., Digit Span, r = .41), and perceptual organization (i.e., Object Assembly, r = .47) (Wechsler, 1997c).

Measures of short term memory:

Three measures of short term verbal memory were administered including a modified administration of the Logical Memory subtest of the WMS-III (Wechsler, 1997b) and two experimental list-learning tasks, Verbal Free Recall and Order Recall.

Logical Memory. A modified administration of the Logical Memory subtest of the WMS-III (Wechsler, 1997a) was used in the present study. For the standard administration, two different stories are presented verbally and individuals are required to recall (verbally) as much of each story as possible following the presentation each story. Story A is heard followed by an immediate recall and then Story B is heard followed by an immediate recall. Story B is then heard again followed by a second immediate recall. There is also a delayed recall component where both stories are recalled 25-35 minutes after immediate recall has been completed. For the present study, in the second session, participants heard the same story (Story A or Story B) twice followed by an immediate recall after each, and a delayed recall 25-35 minutes later. The third session was identical with the exception that the alternate story was heard. This modified administration was employed in order to permit comparison of performance on this task within participants in both glycemic conditions. As indicated earlier, the presentation of the stories was counterbalanced. Stories were presented on a recording as opposed to being read by the tester. This procedure allowed for control of the speed of presentation of each story for

each participant as Shum, Murray, and Eadie (1997) have observed that the recall of story units is dependent on the speed of presentation of the stories on Logical Memory of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987). Participants' recall was also audiotaped to ensure correct recording of their responses. Scoring of this measure was per standard instructions of the WMS-III (Wechsler, 1997a) such that participants received 1 point for each correctly recalled story unit out of a possible 25 story units for each story. The resulting scores were expressed as a percentage of total story units recalled. Reliability of the standard administration of this subtest for adults aged 55 to 89 ranges from r = .81 to .91. Test-retest reliability (from 2 to 12 weeks) for adults aged 55 to 89 has been reported at r = .80 for Logical Memory I (immediate recall) and r = .76 for Logical Memory II (delayed recall). The scoring criteria have an interrater reliability coefficient of $\alpha > .90$ (Wechsler, 1997c). In terms of construct and discriminant validity, scaled scores on Logical Memory have the strongest correlations with other WMS-III measures of verbal memory (i.e., Verbal Paired Associates I, r = .48) and the weakest correlations with non-verbal memory (i.e., Faces I recognition, r = .14) and working memory tasks (i.e., Spatial Span, r = .27) (Wechsler, 1997c).

Verbal Free Recall. This task involved the presentation of 1 practice list of 12 words and 4 experimental lists of 20 words each on a computer screen. Participants were asked to recall as many words from each list immediately following the last word presented and had a total of 2 minutes to recall as many words as possible. The presentation of the lists of words was controlled by the Micro Experimental Laboratory (MEL) software package (version 2.0; Schneider, Rodgers, Mciejczyk, Zuccolotto, & St. James, 1995). The practice and experimental lists were equated on five variables: word

frequency (M = 214 occurrences per million), imagery-evoking value (M = 4.67 on a 7-point scale), number of letters per word (M = 5.32), number of phonemes (M = 4.17), and number of syllables (M = 1.5). The word frequency norms were drawn from the Kucera and Francis (Kucera & Francis, 1967) dictionary and the imagery-evoking values from the MRC Psycholinguistic Database (Coltheart, 1981). The word assignment to lists was controlled for length, frequency of use, and imagery value because these characteristics are the most potent independent variables in word recall (DeLosh & McDaniel, 1996; Paivio & Smythe, 1971). The order of words in each list and the order of the 4 experimental lists were randomized. The presentation of each list was preceded by a 900 Hz 100 ms tone. Each word was displayed on the screen for 1.5 seconds with an interstimulus interval of 200 ms. After the last word of the list was presented, the same 900 Hz 100 ms tone announced the onset of the 2-min recall phase during which participants recalled the items in any order. The total number of words recalled across the four experimental lists resulted in the participant's score on this measure.

Order Recall. This test was similar to Verbal Free Recall and included a practice list of 12 words and two experimental lists of 20 words equated on the same variables: word frequency (M = 159 occurrences per million), imagery-evoking value (M = 4.97), number of letters (M = 5.15), number of phonemes (M = 4.0), and number of syllables (M = 1.55). The procedure used for list presentation was the same as that of Verbal Free Recall. Each word was presented for a duration of 1.5 s with an interstimulus interval of 200 ms. The main difference between the two tasks is that for Order Recall, participants were asked to recall the order of presentation of the words in each list. Thus, they were provided with an alphabetical list of the words in the list that they were required to recall

in the correct order. This test was designed to evaluate memory for contextual-temporal relationship (Shimamura & Squire, 1991) and differs from Verbal Free Recall, as cues were provided for the retrieval of item identity and order information is requested (Nairne, Whiteman, & Woessner, 1995).

Measure of visuospatial functioning:

Rey-Osterrieth Complex Figure and Taylor Complex Figure. The Rey-Osterrieth Complex Figure was designed by Rey (1941) as a measure of perceptual organization and visual memory (Lezak, 1995). The Taylor Complex Figure was developed as an alternate form of the Rey-Osterrieth complex figure to be used in test-retest situations (Lezak, 1995). Thus, for this task, participants viewed either the Rey or Taylor Complex Figure and were asked to copy the figure onto a blank sheet of paper. After participants had copied the figure to the best of their abilities, the stimulus figure and their drawing were immediately removed from their view. They were then asked to draw the figure from memory after a 3-minute delay (i.e., immediate recall phase) and they were not told that they should try to remember the figure, as per standard administration instructions. The delayed recall phase took place 30 minutes after the participant had completed the copy phase and they were again asked to draw the figure from memory.

Measure of central executive functioning:

Modified Brown-Peterson Task. The recall of verbal items is hindered if participants are prevented from engaging in articulatory rehearsal during the retention interval. Morris (Morris, Craik, & Gick, 1990) has shown that recall performance in the classical Brown-Peterson task depends on the requirements of the interpolated task during

the retention interval and the subject's ability to share his attention between the recall task and the interpolated task. Morris used this task successfully to assess attentional and working memory deficits in Alzheimer patients (Morris & Baddeley, 1988). The test used for the present study is a modified, computerized version of the Brown-Peterson Task (Brown, 1958; Peterson & Peterson, 1959). Performance of this task involves the recall of auditory information under conditions of interference and is thus a task of divided attention and working memory that requires central executive functioning. After hearing three consonant letters orally presented by the experimenter (1 second per letter), participants were required to recall the letters in the correct order in writing upon hearing a tone, in 3 conditions of 14 trials each (4 practice and 10 experimental trials). In the baseline condition, participants heard the tone immediately after presentation of the last letter. In the waiting condition, the tone occurred 20 seconds after presentation of the last letter and participants were required to wait silently until they heard the tone before recalling the letters in writing. In the counting condition, participants were orally presented with three consonant letters immediately followed by a 3-digit number. Upon hearing the 3-digit number, participants were required to immediately begin counting backwards from that number by threes until they heard the tone (i.e., after a delay of 20 sec.). At this time, participants recalled the three consonants in writing. This task was scored three ways, each reflecting an average percent of letters recalled correctly across each condition. Firstly, one point was awarded for each correct triad (i.e., all letters correct in the correct order). Next, one point was given for each correctly recalled letter in the correct order. Finally, one point was given for each correctly recalled letter regardless of correct order.

RESULTS

Several statistical analyses were performed to test the four hypotheses of the present study. Eight participants that did not complete all 3 testing sessions were excluded from the analyses. Outliers (i.e., values greater than or less than 3 standard deviations from the mean) in age and/or education were also assessed. One outlier in education was noted, but this subject's data remained in the analyses, as it did not alter the results. In addition to participant drop-outs, random error as a result of researcher, equipment (computer/hardware), or laboratory (blood sampling and measurement) mistakes resulted in isolated missing data points. These missing data points are reflected in the small variations in sample sizes reported in the various analyses conducted.

Descriptive statistics of the participants were run in order to obtain demographic information on age, gender, and education level, glucose regulation values and other biological indices, and scores on the questionnaires and cognitive tests used for screening purposes. Table 1 summarizes the results of these descriptive statistics. Inspection of this table reveals that overall; participants are well-educated, in general good health, and do not show evidence of depression. The majority of participants were female. Exercise was self-reported and defined by participants (i.e., some participants considered housework and gardening to be forms of exercise, while others did not), thus, it is not a reliable measure of exercise and should be interpreted with caution.

Table 1

Demographic and biological data (N=93)

Measure	
Sex	74F / 19 M
Smoker (n)[a]	4
Hormonal Treatment (n)[a]	22
Parental diabetes (n)[a]	21
Age (years)[a]	70.05 ± .86
BMI (kg/m^2)	27.51 ± .50
Education (years)[a]	15.5 ± .33
Exercise (min/week)[a]	571.77 ± 46.4
C Peptide (pmol/l)	831 ± 42.39
Cholesterol (mmol/l)	5.41 ± .09
Triglycerides (mmol/l)	1.41 ± .06
HDL (mmol/l)	1.59 ± .04
LDL (mmol/l)	3.17 ± .08
Cholesterol/HDL cholesterol ratio	3.59 ± .11
Beta-cell function (%)	106.15 ± 6.46
Insulin Sensitivity	2.17 ± .16
Area under the curve (AUCg) (mmol/min)	331.37 ± 21.29
Depressive symptoms (BDI)	4.55 ± .35
MMSE	28.6 ± .13

Note. Values are means ± standard error of the mean (S.E.M.). Beta-cell function (%) and insulin resistance values are obtained from the following equations (Hosker et al., 1985; Mathews et al., 1985): Beta-cell function (%) = 20 x fasting insulin/(fasting glucose-3.5). Insulin resistance = fasting insulin/(22.5 $e^{-\ln(\text{fasting glucose})}$). The incremental area under the curve was calculated as follows: [((g30-g0)/2) x (30-0)] + [{((g30 - g0) + (g60 - g0))/2} x (60 - 30)] + [{((g60 - g0) + (g120 - g0))/2} x (120 - 60)].

[a] Indicates items reported by participants.

Exploratory correlations were conducted in order to observe which glucoregulatory indices appeared to best correlate with cognitive functioning and whether other biological indices (i.e., cholesterol, insulin, c-peptide, and triglycerides) were correlated with cognitive performance. Table 2 summarizes the results of these exploratory correlations and the data are presented separately for the glucose and saccharin conditions. Inspection of this table reveals that age, education, and MMSE scores correlated with all cognitive test results, which are typical findings in this type of sample (Naeveh-Benjamin, Moscovitch, & Roediger, 2001). The BDI correlated with fewer test results and exercise correlated with only Digit-Symbol Coding, Modified Brown-Peterson task (MBP) and Symbol Search.

In addition, it can be observed that the glucose regulation indices based on insulin measures, HOMA indices and in particular, blood glucose measures, were all correlated with cognitive test results. Fewer correlations were observed for cardiovascular risk factor measures (triglycerides, cholesterol, HDL cholesterol, LDL cholesterol, and cholesterol/HDL cholesterol). Inspection of this table also reveals that the majority of correlations between glucose regulation indices and cognitive measures were observed in the saccharin condition. Far fewer correlations were observed for tests conducted after participants drank a glucose solution indicating that glucose ingestion modified the relationship between glucose regulation and cognitive task performance.

Table 2
Summary of exploratory correlations between demographic, biological measures, and performance on neuropsychological tests

	Saccharin		Glucose	
Measure	P<0.01	P<0.05	P<0.01	P<0.05
Age	Arithmetic Digit-Symbol Coding MBP Symbol Search LM 1st recall LM 2nd recall LM 3rd recall LM recognition CF-Delayed L-NS Verbal Free Recall	Digit Span Backward Spatial Span Backward Order recall	Arithmetic Digit-Symbol Coding MBP Symbol Search Spatial Span Backward LM 1st recall LM 2nd recall LM 3rd recall LM recognition CF-Immediate CF-Delayed L-NS Verbal Free Recall	Digit Span Backward
Education	Arithmetic Digit-Symbol Coding Symbol Search Verbal Free Recall	Digit Span Backward LM 2nd recall LM 3rd recall CF-Delayed L-NS Order recall	Arithmetic Digit-Symbol Coding	Symbol Search LM 1st recall LM 3rd recall Verbal Free Recall
BDI		Digit-Symbol Coding Digit Span Forward Spatial Span Backward CF-Copy	Digit-Symbol Coding Spatial Span Forward	
MMSE	Arithmetic MBP Digit Span Backward Symbol Search LM 1st recall LM 2nd recall LM 3rd recall Verbal Free Recall	Digit Span Forward Spatial Span Backward LM recognition CF-Copy Order Recall	Arithmetic Digit-Symbol Coding MBP Digit Span Forward Digit Span Backward Symbol search CF-Immediate CF-Delayed Verbal Free Recall	L-NS Order Recall
Exercise		Digit-Symbol Coding		Digit-Symbol Coding MBP Symbol Search
Fasting glucose				CF-Copy
Glucose 1 h	Digit Span Backward	Arithmetic MBP Spatial span forward L-NS	MBP	
Glucose 2 h	Arithmetic MBP	Digit Span Backward Symbol Search	Arithmetic	MBP
AUC	Arithmetic MBP Digit Span Backward	Spatial Span Forward L-NS	MBP	Arithmetic
Beta-Cell Function		Digit-Symbol Coding		
Insulin Resistance				Arithmetic
Evoked 30 min-fasting	MBP Digit Span Backward		MBP	Digit Span Backward
Evoked 1 hour-fasting	MBP Digit Span Backward	Arithmetic Spatial Span Forward L-NS	MBP	
Peak	MBP Digit Span Backward	Arithmetic Spatial Span Forward Spatial Span Backward L-NS	MBP	Arithmetic

Table 2 (cont.)
Summary of exploratory correlations between demographic, biological measures, and performance on neuropsychological tests

	Saccharin		Glucose	
Measure	P<0.01	P<0.05	P<0.01	P<0.05
Peak-fasting	MBP Digit Span Backward	Arithmetic Spatial Span Forward Spatial Span Backward L-NS	MBP	Arithmetic
Rec 30 min-1 h		Arithmetic Spatial Span Forward		
Rec 2 h-fasting	Arithmetic MBP	Digit Span Backward Symbol Search	Arithmetic	MBP Symbol Search
Rec 30 min – 2 h	Arithmetic			Order Recall
Rec 1 h– 2 h				Order Recall
C-Peptide	Verbal Free Recall	MBP	Verbal Free Recall	
Triglycerides		LM 1st recall LM recognition		
Fasting Ins				Arithmetic
Ins 1 h		Digit-Symbol Coding		Spatial Span Forward
Ins 2 h		Arithmetic Digit Span Backward Order Recall		
Rec Ins 2 h- Fasting Ins	Digit Span Backward	Arithmetic Digit Span Forward Order Recall		
Rec Ins 1 h–Ins 2 h				LM 1st recall
Evoked Ins 1 h–Fasting Ins		Digit-Symbol Coding		Spatial Span Forward
CHOL		LM 1st recall Order Recall		
HDL		L-NS		
LDL		Order Recall		
CHOL/HDL		L-NS		L-NS

Given the observation that glucoregulatory indices based on blood glucose measures, insulin measures, and HOMA indices were all correlated with a number of cognitive tests, it was difficult to choose the glucoregulatory index that appeared to best correlate with cognitive test performance. Therefore, in order to reduce the number of glucoregulatory indices and obtain a more representative glucose regulation variable(s) to examine the relationship between glucose regulation and cognitive performance, a principal components factor analysis with direct oblimin rotation was conducted. Table 3 displays the three components and the glucoregulatory indices from which they are comprised that resulted from this analysis. The three components (i.e., glucose, insulin, and recovery) were named as such as a reflection of the glucoregulatory indices from which they were comprised.

Table 3

Principal Components Analysis

Component 1: Glucose	Weight	Component 2: Insulin	Weight	Component 3: Recovery	Weight
Peak	0.979	Fasting Insulin	0.903	Rec Glucose 0.5h-2h	0.949
Glucose 1h	0.978	Insulin Resistance	0.873	Rec Glucose 2h-fasting	0.778
AUC	0.97	Insulin 1h	0.868	Rec Insulin 1h-2h	0.774
Evoked 1h-fasting	0.966	Evoked Insulin 1h-fasting	0.825	Glucose 2h	-0.744
Peak-fasting	0.965	Betacell	0.821	Rec Glucose 1h-2h	0.72
Glucose 0.5h	0.919	Insulin 2h	0.799		
Evoked 0.5h-fasting	0.876	C-peptide	0.755		
Rec 0.5h-1h	-0.651	Rec Insulin 2h-fasting	0.743		
Fasting glucose	0.592				

In order to investigate the relationship between age, glucose regulation, and performance on the cognitive measures, two sets of analyses were performed on the data.

In the first set of analyses, a series of hierarchical multiple regressions were conducted with glucose regulation (i.e, the abovementioned three components determined by principal components analysis), and age as predictors, and performance on the cognitive tasks as dependent variables. These regressions were conducted separately for the cognitive tests in the glucose and saccharin conditions. The glucose regulation components were each entered into the regression in separate steps (i.e., step 1 = glucose component, step 2 = insulin component, step 3 = recovery component) followed by age (i.e., step 4). Thus, for example, the proportion of variance accounted for by age was that which contributed to the prediction of cognitive performance after the proportion of variance accounted from by glucose regulation had been removed. The glucose regulation components were entered as predictors before age to capitalize on determining any significant relationships, as the prediction of cognitive performance by glucose regulation was most of interest in the present study. The order in which the glucose regulation components were entered was based on the correlational analyses whereby the indices comprising the glucose component were the most highly correlated with cognitive performance and the indices comprising the recovery component were the least highly correlated with cognitive performance. The results of these analyses will be discussed in detail below for each cognitive test.

In the second series of analyses, the data were further analyzed using repeated measures ANOVA. In particular, these analyses allowed for exploration of the interaction between age and glucose regulation on cognitive performance in addition to further examining the effect of solution. The glucose component was the most sensitive predictor (of the glucose regulation components) of cognitive performance in the multiple

regression analyses (see below) and thus, this index was used to categorize participants into two groups using a median split (i.e., participants with better glucose regulation and participants with worse glucose regulation). Age was also observed to be a significant predictor of cognitive performance in the multiple regression analyses (see below). It was also hypothesized that age would interact with glucose regulation to impact cognitive performance therefore; using a median split, we further divided our participants into younger (55-72 years) and older (>72 years) groups.

The demographics and biological characteristics of these groups are presented in Table 4. Across the four groups, the gender distribution was similar. In addition, the number of smokers, the number of participants taking hormonal treatment, and the number of participants who reported diabetes in their parents was similar across the four groups. The other data presented in Table 4 were analyzed using one-way ANOVA followed by Tukey's HSD tests when necessary. There was a significant difference between age groups ($F(3,89) = 63.789$, $P < .001$) showing that the median split procedure was successful. There were also significant differences between glucoregulatory groups on all glucose measures (i.e., fasting glucose, glucose 30-minutes, glucose 1-hour, glucose 2-hour, peak glucose, AUC) with participants with worse glucose regulation having significantly higher values. Fasting insulin and insulin 1-hour were not significantly different between glucoregulatory groups although participants with worse glucose regulation tended to have higher values than participants with better glucose regulation. Older participants with worse glucose regulation had significantly higher insulin 2-hour values than younger than participants with better glucose regulation (in both age groups). Younger participants with worse glucose regulation had significantly

higher 2-hour insulin values than younger participants with better glucose regulation. There was a trend for younger participants with better regulation to have lower insulin resistance values than older participants with worse regulation. Among those with worse regulation, younger participants had significantly lower AUC values and significantly higher cholesterol ratios than older participants.

Table 4
Demographic and Biological Data as a Function of Glucoregulatory Status and Age

Measure	Better Regulators		Worse Regulators	
	Younger	Older	Younger	Older
Sex	5M / 22F	5M / 15F	7M / 18 F	2M / 19 F
Smoker	1	0	2	1
Hormonal Treatment	9	2	6	5
Parental Diabetes	7	3	6	5
Age (years)	62.7 ± 1.04	77.8 ± .76	65.6 ± 1.1	77.5 ± .84
Education (years)	15.9 ± .61	15.7 ± .71	16.1 ± .65	14 ± .58
Depressive symptoms (BDI)	3.8 ± .72	4.7 ± .68	3.9 ± .48	6.2 ± .79
MMSE	28.8 ± .23	28.6 ± .25	28.9 ± .26	28 ± .26
BMI (kg/m2)	26.9 ± 1.1	27 ± .67	29.2 ± 1.1	26.7 ± .88
Exercise (min/week)	465.9 ± 57	477.9 ± 65.8	697.7 ± 115	647.4 ± 115
Glucose fasting	5.041 ± .07	5.145 ± .16	5.424 ± .08	5.471 ± .12
Glucose30 minutes	7.526 ± .20	7.655 ± . 27	10.168 ± .19	10.457 ± .34
Glucose 1-hour	6.874 ± .33	6.680 ± .29	10.476 ± .32	11.633 ± .46
Glucose 2-hour	5.967 ± .24	6.035 ± .39	7.656 ± .42	9.481 ± .72
Peak Glucose	7.826 ± .22	7.935 ± .26	10.9 ± .26	12.029 ± .48
Insulin fasting	54.22 ± 7.5	56.8 ± 4.7	71.36 ± 8.7	81.86 ± 12.6
Insulin 1-hour	505.81 ± 81.5	428.55 ± 40.6	660.76 ± 62.4	674.52 ± 114.8
Insulin 2-hour	338.96 ± 30.8	365.25 ± 41.4	604.28 ± 66.6	724.24 ± 107.6
c-Peptide (pmol/l)	666.3 ± 57.9	868.3 ± 101.1	897.8 ± 93.1	927.7 ± 82.7
Cholesterol (mmol/l)	5.4 ± .17	54. ± .19	5.7 ± .17	5.1 ± .19
Triglycerides (mmol/l)	1.4 ± .12	1.3 ± .07	1.6 ± .16	1.2 ± .11
HDL cholesterol (mmol/l)	1.6 ± .06	1.5 ± .09	1.6 ± .1	1.7 ± .12
LDL cholesterol (mmol/l)	3.2 ± .14	3.3 ± .16	3.4 ± .15	2.8 ± .19
Cholesterol/HDL cholesterol ratio	3.4 ± .18	3.7 ± .2	4.0 ± .24	3.2 ± .19
Beta-cell function (%)	96.4 ± 11.8	108.4 ± 13	108.3 ± 14	114 ± 13.3
Insulin sensitivity	1.7 ± .26	1.8 ± .16	2.4 ± .29	2.8 ± .48
Area under the curve (AUCg) (mmol/l/min)	184.8 ± 20.6	171.1 ± 20.9	436.6 ±24.6	547.1 ± 41

Note. Values are means ± standard error of the mean (S.E.M.). Beta-cell function (%) and insulin resistance values are obtained from the following equations (Hosker et al., 1985; Mathews et al., 1985): Beta-cell function (%) = 20 x fasting insulin/(fasting glucose-3.5). Insulin resistance = fasting insulin/(22.5 e-ln(fasting glucose)). The incremental area under the curve was calculated as follows: [((g30-g0)/2) x (30-0)] + [{((g30 - g0) + (g60 - g0))/2} x (60 - 30)] + [{((g60 - g0) + (g120 - g0))/2} x (120 - 60)].

[a] Indicates items reported by participants.

Older participants tended to have more depressive symptomatology, but this finding was not significant ($F(3,89) = 2.587$, $P = .058$). Moreover, depressive symptomatology fell within the minimal range on the BDI for all four groups. Among participants with worse regulation, there was a trend for older participants to have lower MMSE scores than younger participants. However, MMSE scores fell within the normal range for all four groups.

As indicated above, the results from the multiple regression analyses are presented for each test. Tables 5a and 5b can be referred to, as they present an overview of the results of the regression models for each cognitive test for the saccharin and glucose conditions, respectively. Similarly, Tables 6a and 6b display the semi-partial correlations and beta coefficients for each cognitive test for the saccharin and glucose conditions, respectively. In addition, the results from the repeated measures ANOVA analysis are presented. Specifically, the data were analyzed using three-way ANOVAs with age (younger vs. older) and glucose regulation (better vs. worse) as between-subjects variables and solution (saccharin vs. glucose) as the within-subjects variable.

Table 5a
Multiple Regressions: Saccharin Condition

Test	Step	Adjusted R^2	F_{inc}	p
Arithmetic	1	.039	4.741	.032
	2	.038	.908	ns
	3	.088	5.941	.017
	4	.164	9.047	.003
D-SC	1	.007	1.657	ns
	2	.031	3.247	ns
	3	.020	.011	ns
	4	.191	19.787	.001
MBP	1	.075	8.500	.004
	2	.078	1.241	ns
	3	.069	.190	ns
	4	.158	10.344	.002
Symbol Search	1	.007	1.663	ns
	2	-.004	.011	ns
	3	-.001	1.205	ns
	4	.183	21.143	.001
DS Forward	1	.009	1.860	ns
	2	.000	.114	ns
	3	-.012	.003	ns
	4	.002	2.216	ns
DS Backward	1	.097	10.837	.001
	2	.087	.009	ns
	3	.077	.021	ns
	4	.114	4.772	.032
SS Forward	1	.036	4.457	.038
	2	.030	.432	ns
	3	.021	.140	ns
	4	.011	.085	ns
SS Backward	1	.030	3.880	.052 (trend)
	2	.020	.008	ns
	3	.014	.513	ns
	4	.036	3.046	ns
LN-S	1	.038	4.632	.034
	2	.030	.222	ns
	3	.019	.031	ns
	4	.172	17.385	.001
LM1	1	.003	1.250	ns
	2	-.002	.535	ns
	3	-.012	.121	ns
	4	.183	22.223	.001
LM2	1	.013	2.201	ns
	2	.006	.400	ns
	3	-.002	.216	ns
	4	.164	18.747	.001
LM3	1	.005	1.462	ns
	2	.010	1.463	ns
	3	-.001	.002	ns
	4	.150	16.857	.001

Note. Step 1=Model 1 with Gluc; Step 2=Model 2 with Ins; Step 3=Model 3 with Recov; Step 4= Model 4 with Age; DS-C=Digit-Symbol Coding; DS=Digit Span; SS=Spatial Span; LN-S=Letter-number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall; LM3= Logical Memory 3rd recall; CF Copy=Complex Figure Copy; CF Immediate=Complex Figure Immediate Recall; CF Delayed=Complex Figure Delayed Recall;VFR=Verbal Free Recall; OR= Order Recall; ns=not sigificant

Table 5a (cont.)
Multiple Regressions: Saccharin Condition

Test	Step	R^2	F_{inc}	p
LMREC	1	-.008	.306	ns
	2	-.010	.810	ns
	3	-.016	.413	ns
	4	.051	7.334	.008
CF Copy	1	-.007	.316	ns
	2	.013	2.930	ns
	3	.014	1.019	ns
	4	.027	2.211	ns
CF Immediate	1	-.011	.001	ns
	2	-.021	.080	ns
	3	-.032	.103	ns
	4	.002	4.040	.047
CF Delayed	1	-.007	.406	ns
	2	-.017	.061	ns
	3	-.028	.080	ns
	4	.042	7.466	.008
VFR	1	.022	3.037	ns
	2	.012	.099	ns
	3	.003	.223	ns
	4	.237	27.956	.000
OR	1	.007	1.602	ns
	2	.005	.898	ns
	3	-.005	.049	ns
	4	.023	3.557	ns

Note. Step 1=Model 1 with Gluc; Step 2=Model 2 with Ins; Step 3=Model 3 with Recov; Step 4= Model 4 with Age; DS-C=Digit-Symbol Coding; DS=Digit Span; SS=Spatial Span; LN-S=Letter-number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall; LM3= Logical Memory 3rd recall; CF Copy=Complex Figure Copy; CF Immediate=Complex Figure Immediate Recall; CF Delayed=Complex Figure Delayed Recall;VFR=Verbal Free Recall; OR= Order Recall; ns=not sigificant

Table 5b
Multiple Regressions: Glucose Condition

Test	Step	Adjusted R^2	F_{inc}	p
Arithmetic	1	.033	4.158	.044
	2	.039	1.597	ns
	3	.049	1.915	ns
	4	.115	7.663	.007
D-SC	1	.004	1.374	ns
	2	-.002	.456	ns
	3	-.01	.289	ns
	4	.226	28.153	.000
MBP	1	.088	9.842	.002
	2	.078	.068	ns
	3	.069	.140	ns
	4	.247	22.011	.000
Symbol Search	1	.015	2.440	ns
	2	.005	.079	ns
	3	.012	1.615	ns
	4	.335	44.194	.000
DS Forward	1	.009	.842	ns
	2	.018	.803	ns
	3	.020	.149	ns
	4	.054	3.195	ns
DS Backward	1	.021	2.939	ns
	2	.011	.120	ns
	3	.008	.681	ns
	4	.047	4.725	.032
SS Forward	1	-.010	.113	ns
	2	.004	2.238	ns
	3	-.003	.411	ns
	4	.001	1.349	ns
SS Backward	1	-.008	.246	ns
	2	-.017	.188	ns
	3	-.024	.405	ns
	4	.052	8.188	.005
LN-S	1	-.005	.562	ns
	2	-.003	1.183	ns
	3	-.014	.021	ns
	4	.148	17.961	.000
LM1	1	.007	1.656	ns
	2	-.004	.007	ns
	3	-.005	.873	ns
	4	.109	12.363	.001

Note. Step 1=Model 1 with Gluc; Step 2=Model 2 with Ins; Step 3=Model 3 with Recov; Step 4= Model 4 with Age; DS-C=Digit-Symbol Coding; DS=Digit Span; SS=Spatial Span; LN-S=Letter-number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall; LM3= Logical Memory 3rd recall; CF Copy=Complex Figure Copy; CF Immediate=Complex Figure Order Recall; ns=not sigificant

Table 5b (cont.)
Multiple Regressions: Glucose Condition

Test	Step	R^2	F_{inc}	p
LM2	1	-.010	.100	ns
	2	-.021	.009	ns
	3	-.030	.206	ns
	4	.123	16.551	.000
LM3	1	-.006	.409	ns
	2	-.018	.001	ns
	3	-.029	.002	ns
	4	.107	14.611	.000
LMREC	1	-.010	.112	ns
	2	-.005	1.461	ns
	3	-.007	.784	ns
	4	.071	8.461	.005
CF Copy	1	-.003	.755	ns
	2	-.011	.240	ns
	3	-.021	.151	ns
	4	-.032	.002	ns
CF Immediate	1	.000	1.006	ns
	2	-.010	.130	ns
	3	-.017	.382	ns
	4	.065	8.729	.004
CF Delayed	1	-.001	.947	ns
	2	-.009	.224	ns
	3	-.017	.284	ns
	4	.114	14.154	.000
VFR	1	-.002	.800	ns
	2	-.002	.982	ns
	3	-.011	.200	ns
	4	.161	19.113	.000
OR	1	.010	1.964	ns
	2	.017	1.621	ns
	3	.025	1.728	ns
	4	.036	2.063	ns

Note. Step 1=Model 1 with Gluc; Step 2=Model 2 with Ins; Step 3=Model 3 with Recov; Step 4 Model 4 with Age; DS-C=Digit-Symbol Coding; DS=Digit Span; SS=Spatial Span; LN-S=Letter-number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall; LM3= Logical Memory 3rd recall; CF Copy=Complex Figure Copy; CF Immediate=Complex Figure Immediate Recall; CF Delayed=Complex Figure Delayed Recall;VFR=Verbal Free Recall; OR= Order Recall; ns=not sigificant

Table 6a
Betas and Semi-Partial Correlations: Saccharin Condition

	Model 1		Model 2				Model 3					
	GLUC		GLUC		INS		GLUC		INS		RECOV	
Test	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta
ARITH	-0.223	-0.223	-0.193	-0.199	-0.097	-0.1	-0.151	-0.158	-0.093	-0.096	0.243	0.246
D-SC	-0.134	-0.134	-0.086	-0.089	-0.185	-0.19	-0.087	-0.091	-0.185	-0.191	-0.011	-0.011
MBP	-0.292	-0.292	-0.258	-0.265	-0.112	-0.115	-0.247	-0.258	-0.111	-0.114	0.044	0.045
SS	-0.134	-0.134	-0.128	-0.131	-0.011	-0.011	-0.107	-0.112	-0.009	-0.009	0.115	0.116
DSF	-0.142	-0.142	-0.129	-0.133	-0.035	-0.036	-0.128	-0.134	-0.035	-0.036	-0.006	-0.006
DSB	-0.326	-0.326	-0.315	-0.324	-0.009	-0.01	-0.313	-0.313	-0.01	-0.01	-0.015	-0.015
SSF	-0.216	-0.216	-0.226	-0.233	0.067	0.069	-0.217	-0.226	0.068	0.07	0.039	0.039
SSB	-0.202	-0.202	-0.199	-0.205	0.009	0.01	-0.184	-0.192	0.011	0.011	0.074	0.075
L-NS	-0.22	-0.22	-0.202	-0.208	-0.048	-0.05	-0.203	-0.211	-0.049	-0.05	-0.018	-0.018
LM1	-0.116	-0.116	-0.095	-0.098	-0.076	-0.079	-0.088	-0.092	-0.076	-0.078	0.037	0.037
LM2	-0.154	-0.154	-0.134	-0.138	-0.066	-0.068	-0.14	-0.146	-0.067	-0.069	-0.049	-0.049
LM3	-0.126	-0.126	-0.092	-0.095	-0.125	-0.129	-0.092	-0.096	-0.126	-0.129	-0.005	-0.005
LMREC	-0.058	-0.058	-0.034	-0.035	-0.094	-0.097	-0.044	-0.046	-0.095	-0.098	-0.068	-0.069
CFC	0.059	0.059	0.015	0.016	0.177	0.182	-0.002	-0.002	0.175	0.181	-0.105	-0.106
CFI	-0.002	-0.002	0.005	0.005	-0.03	-0.031	0	0	-0.03	-0.031	-0.034	-0.035
CFD	-0.067	-0.067	-0.071	-0.073	0.026	0.027	-0.075	-0.078	0.025	0.026	-0.03	-0.03
VFR	-0.181	-0.181	-0.183	-0.189	0.033	0.034	-0.189	-0.197	0.032	0.033	-0.049	-0.05
OR	-0.132	-0.132	-0.103	-0.107	-0.099	-0.102	-0.106	-0.111	-0.099	-0.102	-0.023	-0.024

Note. ARITH=Arithmetic, DS-C=Digit-Symbol Coding; MBP=Modified Brown Peterson Task; SS=Symbol Search; DSF=Digit Span Forward; DSB=Digit Span Backward; SSF=Spatial Span Forward; SSB=Spatial Span Backward; L-NS=Letter-Number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall;LM3=Logical Memory 3rd recall; CFC=Complex Figure Copy; CFI=Complex Figure Immediate Recall; CFD=Complex Figure Delayed Recall; VFR=Verbal Free Recall; OR=Order Recall; GLUC=Glucose component; INS=Insulin Component; RECOV= Recovery Component; *p<05; **p<.01; ***p<.001; +=trend;

Table 6a (cont.)
Betas and Semi-Partial Correlations: Saccharin Condition

Model 4							
GLUC		INS		RECOV		AGE	
Sr^2	Beta	Sr^2	Beta	Sr^2	Beta	Sr^2	Beta
-0.134	-0.14	-0.053	-0.055	0.21	0.214	-0.287	-0.293
-0.062	-0.065	-0.126	-0.131	-0.057	-0.058	-0.417	-0.427
-0.228	-0.239	-0.067	-0.07	0.01	0.01	-0.308	-0.315
-0.081	-0.085	0.051	0.053	0.066	0.068	-0.433	-0.443
-0.119	-0.124	-0.014	-0.014	-0.023	-0.024	-0.155	-0.159
-0.3	-0.313	0.02	0.021	-0.041	-0.039	-0.227	-0.219
-0.215	-0.224	0.072	0.074	0.035	0.036	-0.03	-0.031
-0.173	-0.181	0.035	0.037	0.054	0.055	-0.179	-0.183
-0.179	-0.187	0.006	0.007	-0.062	-0.063	-0.396	-0.405
-0.061	-0.064	-0.014	-0.014	-0.013	-0.013	-0.444	-0.454
-0.115	-0.12	-0.009	-0.009	-0.094	-0.096	-0.413	-0.422
-0.068	-0.071	-0.07	-0.073	-0.048	-0.049	-0.395	-0.403
-0.028	-0.029	-0.056	-0.059	-0.097	-0.099	-0.275	-0.281
0.007	0.008	0.195	0.203	-0.121	-0.123	-0.153	-0.156
0.012	0.013	-0.001	-0.001	-0.057	-0.058	-0.209	-0.214
-0.058	-0.061	0.064	0.066	-0.06	-0.062	-0.279	-0.285
-0.161	-0.168	0.096	0.099	-0.103	-0.105	-0.484	-0.494
-0.099	-0.104	-0.069	-0.072	-0.047	-0.048	-0.195	-0.2

Note. ARITH=Arithmetic, DS-C=Digit-Symbol Coding; MBP=Modified Brown Peterson Task; SS=Symbol Search; DSF=Digit Span Forward; DSB=Digit Span Backward; SSF=Spatial Span Forward; SSB=Spatial Span Backward; L-NS=Letter-Number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall;LM3=Logical Memory 3rd recall; CFC=Complex Figure Copy; CFI=Complex Figure Immediate Recall; CFD=Complex Figure Delaye Recall; VFR=Verbal Free Recall; OR=Order Recall; GLUC=Glucose component; INS=Insulin Component; RECOV= Recovery Component; *p<05; **p<.01; ***p<.001; +=trend;

Table 6b
Betas and Semi-Partial Correlations: Glucose Condition

	Model 1		Model 2				Model 3					
	GLUC		GLUC		INS		GLUC		INS		RECOV	
Test	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta
ARITH	-0.209	-0.209	-0.173	-0.178	-0.129	-0.133	-0.148	-0.154	-0.127	-0.13	0.141	0.143
D-SC	-0.122	-0.122	-0.102	-0.105	-0.07	-0.072	-0.091	-0.095	-0.069	-0.072	0.056	0.057
MBP	-0.312	-0.312	-0.297	-0.306	-0.026	-0.027	-0.3	-0.312	-0.027	-0.028	-0.038	-0.038
SS	-0.162	-0.162	-0.15	-0.154	-0.029	-0.03	-0.127	-0.132	-0.027	-0.028	0.132	0.134
DSF	-0.096	-0.096	-0.071	-0.073	-0.094	-0.096	-0.077	-0.08	-0.094	-0.097	-0.041	-0.041
DSB	-0.177	-0.177	-0.18	-0.186	0.036	0.037	-0.192	-0.2	0.035	0.036	-0.086	-0.087
SSF	-0.035	-0.035	-0.071	-0.073	0.156	0.16	-0.059	-0.062	0.157	0.161	0.067	0.068
SSB	-0.052	-0.052	-0.04	-0.041	-0.046	-0.047	-0.05	-0.052	-0.047	-0.048	-0.067	-0.068
L-NS	-0.078	-0.078	-0.049	-0.051	-0.114	-0.117	-0.053	-0.053	-0.114	-0.117	-0.015	-0.015
LM1	-0.134	-0.134	-0.128	-0.132	-0.009	-0.009	-0.11	-0.115	-0.007	-0.007	0.098	-0.099
LM2	-0.033	-0.033	-0.03	-0.031	-0.01	-0.011	-0.037	-0.039	-0.011	-0.011	-0.048	-0.049
LM3	-0.067	-0.067	-0.064	-0.066	-0.004	-0.004	-0.064	-0.067	-0.004	-0.004	-0.005	-0.005
LMREC	-0.035	-0.035	-0.004	-0.004	-0.126	-0.13	0.011	0.011	-0.125	-0.128	0.093	0.094
CFC	-0.091	-0.091	-0.1	-0.103	0.051	0.053	-0.106	-0.11	0.051	0.052	-0.041	-0.042
CFI	-0.105	-0.105	-0.111	-0.114	0.038	0.039	-0.099	-0.103	0.039	0.04	0.065	0.066
CFD	-0.101	-0.101	-0.11	-0.114	0.05	0.051	-0.1	-0.104	0.05	0.052	0.056	0.057
VFR	-0.094	-0.094	-0.067	-0.068	-0.104	-0.107	-0.073	-0.076	-0.105	-0.108	-0.047	-0.048
OR	-0.145	-0.145	-0.11	-0.113	-0.132	-0.135	-0.13	-0.136	-0.134	-0.138	-0.135	-0.137

Note. ARITH=Arithmetic, DS-C=Digit-Symbol Coding; MBP=Modified Brown Peterson Task; SS=Symbol Search; DSF=Digit Span Forward; DSB=Digit Span Backward; SSF=Spatial Span Forward; SSB=Spatial Span Backward; L-NS=Letter-Number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall;LM3=Logical Memory 3rd recall; CFC=Complex Figure Copy; CFI=Complex Figure Immediate Recall; CFD=Complex Figure Delayed Recall; VFR=Verbal Free Recall; OR=Order Recall; GLUC=Glucose component; INS=Insulin Component; RECOV= Recovery Component; *p<05; **p<.01; ***p<.001; +=trend;

Table 6b (cont.)
Betas and Semi-Partial Correlations: Glucose Condition

Model 4							
GLUC		INS		RECOV		AGE	
Sr2	Beta	Sr2	Beta	Sr2	Beta	Sr2	Beta
-0.131	-0.137	-0.088	-0.091	0.11	0.112	-0.271	-0.278
-0.062	-0.065	-0.002	-0.002	0.002	0.002	-0.487	-0.498
-0.274	-0.286	0.032	0.033	-0.084	-0.086	-0.424	-0.434
-0.093	-0.097	0.051	0.053	0.069	0.07	-0.565	-0.578
-0.065	-0.068	-0.068	-0.07	-0.061	-0.062	-0.185	-0.19
-0.178	-0.186	0.065	0.067	-0.11	-0.112	-0.221	-0.226
-0.052	-0.054	0.172	0.179	0.053	0.054	-0.121	-0.124
-0.033	-0.034	-0.006	-0.006	-0.099	-0.101	-0.299	-0.297
-0.027	-0.028	-0.056	-0.059	-0.06	-0.061	-0.408	-0.417
-0.09	-0.094	0.041	0.042	0.059	0.06	-0.346	-0.354
-0.013	-0.014	0.044	0.046	-0.091	-0.093	-0.397	-0.406
-0.042	-0.043	0.048	0.05	-0.047	-0.048	-0.376	-0.385
0.028	0.029	-0.083	-0.086	0.06	0.061	-0.292	-0.299
-0.105	-0.11	0.051	0.053	-0.041	-0.042	-0.005	-0.005
-0.081	-0.084	0.08	0.083	0.032	0.032	-0.298	-0.305
-0.078	-0.081	0.101	0.105	0.015	0.015	-0.369	-0.378
-0.048	-0.051	-0.043	-0.045	-0.088	-0.09	-0.42	-0.429
-0.121	-0.127	-0.112	-0.117	-0.151	-0.154	-0.147	-0.15

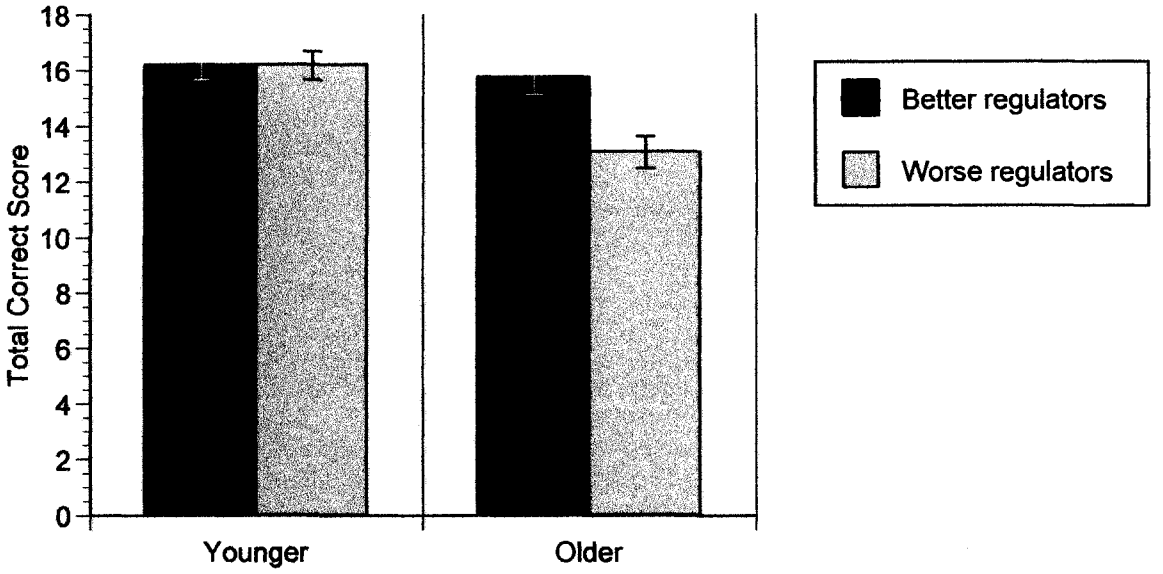
Note. ARITH=Arithmetic, DS-C=Digit-Symbol Coding; MBP=Modified Brown Peterson Task; SS=Symbol Search; DSF=Digit Span Forward; DSB=Digit Span Backward; SSF=Spatial Span Forward; SSB=Spatial Span Backward; L-NS=Letter-Number sequencing; LM1=Logical Memory 1st recall; LM2=Logical Memory 2nd recall;LM3=Logical Memory 3rd recall; CFC=Complex Figure Copy; CFI=Complex Figure Immediate Recall; CFD=Complex Figure Delaye Recall; VFR=Verbal Free Recall; OR=Order Recall; GLUC=Glucose component; INS=Insulin Component; RECOV= Recovery Component; *p<05; **p<.01; ***p<.001; +=trend;

Measures of Attentional Processes and Working Memory:

Arithmetic. The results from the multiple regression indicate that in the saccharin condition, the glucose component was a significant predictor of Arithmetic performance after step 1 ($R^2 = .039$; $F_{inc}(1,91) = 4.741$, $p < .05$), the recovery component was a significant predictor after step 3 ($R^2 = .088$; $F_{inc}(1, 89) = 5.941$, $p < .05$), and age was a significant predictor after step 4 ($R^2 = .166$; $F_{inc}(1,88) = 9.047$, $p < .01$). These results indicate that increasing age and worse glucose regulation was associated with decreased Arithmetic performance. In the glucose condition, the glucose component was a significant predictor of Arithmetic performance after step 1 ($R^2 = .033$; $F_{inc}(1,91) = 4.158$, $p < .05$), and age was a significant predictor of performance after step 4 ($R^2 = .033$; $F_{inc}(1,88) = 7.663$, $p < .01$). Specifically, increasing age and worse glucose regulation was associated with decreased performance.

The results of the ANOVA indicated that there was a significant main effect of age ($F(1, 89) = 10.660$, $p < .01$) and a significant main effect of glucose regulation ($F(1, 89) = 5.923$, $p < .05$). Participants with better glucose regulation performed significantly better than those with worse glucose regulation, and younger participants performed significantly better than older participants on this task. There was also a significant interaction between age and glucose regulation ($F(1, 89) = 6.042$, $p < .05$). Tukey's HSD tests showed that older participants with worse glucose regulation performed significantly worse than the other three groups, irrespective of solution. Figure 1 shows the results for the four groups.

Figure 1. Arithmetic Performance



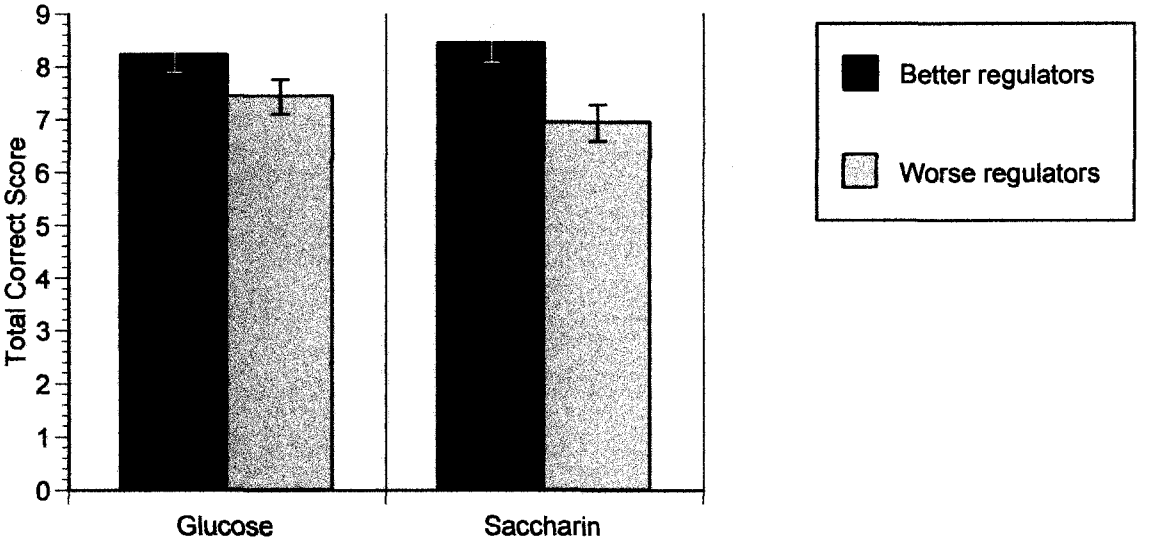
Digit Span. The multiple regression and ANOVA results for Digit Span Forward did not reveal any significant findings.

The multiple regression results for Digit Span Backward indicate that in the saccharin condition, the glucose component was a significant predictor of performance after step 1 ($R^2 = .097$; $F_{inc}(1,91) = 10.837$, $p < .01$), and age was a significant predictor after step 4 ($R^2 = .114$; $F_{inc}(1,88) = 4.772$, $p < .05$). Specifically, increasing age and worse glucose regulation were associated with decreased performance. In the glucose condition, age was a significant predictor of Digit Span Backward performance after step 4 ($R^2 = .047$; $F_{inc}(1,88) = 4.725$, $p < .05$). Specifically, increasing age was associated with decreased performance.

The ANOVA showed a significant main effect of glucose regulation ($F(1, 89) = 6.734$, $p < .05$), and a trend for a main effect of age ($F(1, 89) = 3.530$, $p = .064$). Participants with better glucose regulation performed significantly better than those with

worse glucose regulation, and younger participants performed better than older participants on this task. There was also a trend for a significant interaction between glucose regulation and solution ($F(1, 89) = 3.890$, $p = .052$). Tukey's HSD tests showed that better regulators in the glucose condition performed better than worse regulators in the saccharin condition. Figure 2 shows the results for the four groups.

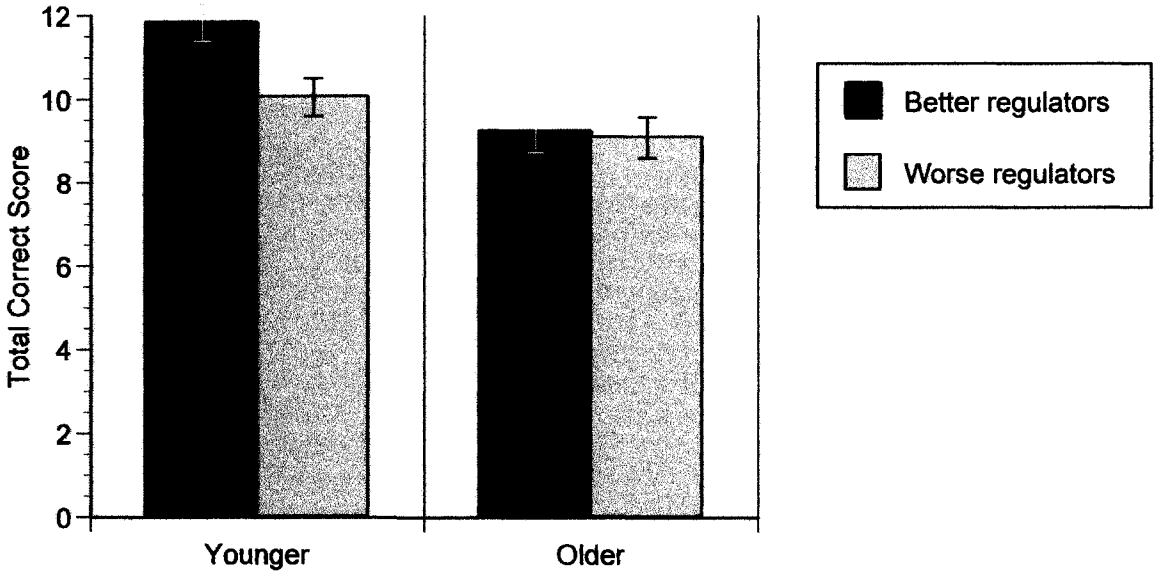
Figure 2. Digit Span Backward Performance



Letter-Number Sequencing. The results from the multiple regression indicate that in the saccharin condition, the glucose component was a significant predictor of Letter-Number Sequencing performance after step 1 ($R^2 = .038$; $F_{inc}(1,91) = 4.632$, $p < .05$), and age was a significant predictor after step 4 ($R^2 = .172$; $F_{inc}(1,88) = 17.385$, $p < .001$). These results indicate that increasing age and worse glucose regulation was associated with decreased Letter-Number Sequencing performance. In the glucose condition, the multiple regression results for Letter-Number Sequencing indicate that age was a significant predictor of performance after step 4 ($R^2 = .148$; $F_{inc}(1,88) = 17.961$, $p < .001$). Specifically, increasing age was associated with decreased performance.

The results of the ANOVA indicated that there was a significant main effect of age ($F(1, 89) = 14.077$, $p < .001$), and a significant main effect of glucose regulation ($F(1, 89) = 4.157$, $p < .05$). Participants with better glucose regulation performed significantly better than those with worse glucose regulation, and younger participants performed significantly better than older participants on this task. There was also a trend for significant interaction between age and glucose regulation ($F(1, 89) = 2.927$, $p = .09$). Tukey's HSD tests showed that younger participants with better glucose regulation performed better than the other three groups, irrespective of solution. Figure 3 shows the results for the four groups.

Figure 3. Letter-Number Sequencing Performance



Spatial Span. The results from the multiple regression indicate that in the saccharin condition, the glucose component was a significant predictor of Spatial Span Forward performance after step 1 ($R^2 = .036$; $F_{inc}(1,91) = 4.457$, $p < .05$. These results

indicate that worse glucose regulation was associated with decreased Spatial Span Forward performance. The ANOVA did not reveal any significant findings.

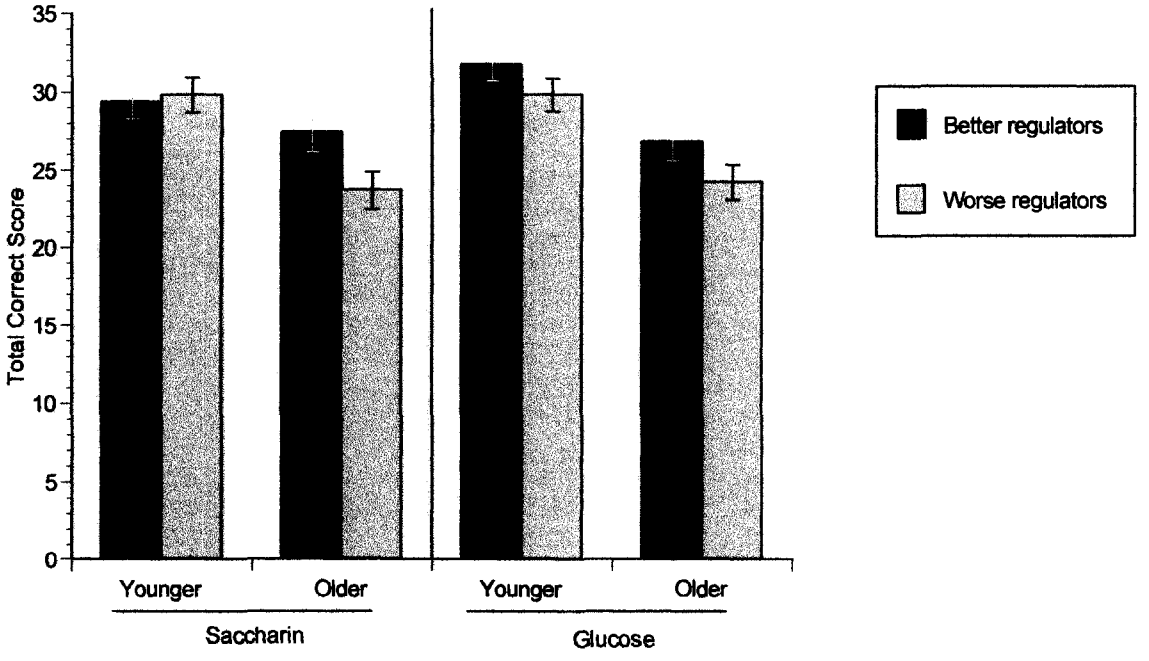
The multiple regression results for Spatial Span Backward in the saccharin condition indicate that there was a trend for the glucose component in predicting performance after step 1 ($R^2 = .030$; $F_{inc}(1,91) = 3.880$, $p = .052$). Specifically, worse glucose regulation was associated with decreased performance. In the glucose condition, the multiple regression results for Spatial Span Backward indicate that age was a significant predictor of performance after step 4 ($R^2 = .052$; $F_{inc}(1,88) = 8.188$, $p < .01$). Specifically, increasing age was associated with decreased performance. The results of the ANOVA indicated that there was a significant main effect of age ($F(1, 89) = 4.632$, $p < .05$). Younger participants performed significantly better than older participants on this task.

Symbol Search. The results from the multiple regression indicate that in the saccharin condition, age was a significant predictor of Symbol Search performance after step 4 ($R^2 = .183$; $F_{inc}(1,88) = 21.143$, $p < .001$). These results indicate that increasing age was associated with decreased Symbol Search performance. In the glucose condition, the multiple regression results for Symbol Search indicate that age was a significant predictor of performance after step 4 ($R^2 = .335$; $F_{inc}(1,88) = 44.194$, $p < .001$). Specifically, increasing age was associated with decreased performance.

The results of the ANOVA indicated that there was a significant main effect of age ($F(1, 89) = 13.871$, $p < .001$), a trend for a main effect of glucose regulation ($F(1, 89) = 3.249$, $p = .075$). Participants with better glucose regulation performed better than those with worse glucose regulation, and younger participants performed significantly

better than older participants on this task. There was also a significant interaction between age, glucose regulation, and solution ($F(1, 89) = 6.667$, $p < .05$). Tukey's HSD tests showed that younger participants with better glucose regulation in the glucose condition performed better than younger participants with better glucose regulation in the saccharin condition and older participants with worse regulation in both the saccharin and glucose conditions. Older participants with worse regulation in the glucose condition also performed significantly worse than younger better regulators and younger worse regulators in the saccharin condition. Older participants with worse regulation in the saccharin condition performed more poorly than younger worse regulators in the glucose condition. Figure 4 shows the results for the four groups in both the saccharin and glucose conditions.

Figure 4. Symbol Search Performance



Digit-Symbol Coding. The results from the multiple regression indicate that in the saccharin condition, age was a significant predictor of Digit-Symbol Coding performance

after step 4 ($R^2 = .191$; $F_{inc}(1,88) = 19.787$, $p < .001$). These results indicate that increasing age was associated with decreased Digit-Symbol Coding performance. In the glucose condition, the multiple regression results for Digit-Symbol Coding indicate that age was a significant predictor of performance after step 4 ($R^2 = .226$; $F_{inc}(1,88) = 28.153$, $p < .001$). Specifically, increasing age was associated with decreased performance.

The ANOVA showed a significant main effect of age ($F(1, 89) = 9.925$, $p < .01$), and a trend for a main effect of glucose regulation ($F(1, 89) = 3.844$, $p = .053$). Participants with better glucose regulation performed better than those with worse glucose regulation, and younger participants performed significantly better than older participants on this task.

Measures of Short Term Memory:

Logical Memory. The results from the multiple regression indicate that in the saccharin condition, age was a significant predictor of Logical Memory 1st recall performance after step 4 ($R^2 = .183$; $F_{inc}(1,88) = 22.223$, $p < .001$). Similarly, in the saccharin condition, age was a significant predictor of Logical Memory 2nd recall performance after step 4 ($R^2 = .164$; $F_{inc}(1,88) = 18.747$, $p < .001$), Logical Memory 3rd recall performance after step 4 ($R^2 = .150$; $F_{inc}(1,88) = 16.857$, $p < .001$), and Logical Memory Recognition performance after step 4 ($R^2 = .051$; $F_{inc}(1,88) = 7.334$, $p < .01$). In all cases, increasing age was associated with decreased performance.

In the glucose condition, the multiple regression results indicate that age was a significant predictor of Logical Memory 1st recall performance after step 4 ($R^2 = .109$; $F_{inc}(1,88) = 12.363$, $p < .01$), Logical Memory 2nd recall performance after step 4 ($R^2 =$

.123; $F_{inc}(1,88) = 16.551$, $p < .001$), Logical Memory 3rd recall performance after step 4 ($R^2 = .107$; $F_{inc}(1,88) = 14.611$, $p < .001$), and Logical Memory Recognition performance after step 4 ($R^2 = .071$; $F_{inc}(1,88) = 8.461$, $p < .01$). In all cases, increasing age was associated with decreased performance.

The results of the ANOVA indicated that there was a significant main effect of age for Logical Memory 1st recall ($F(1, 89) = 14.503$, $p < .001$), Logical Memory 2nd recall ($F(1, 89) = 11.077$, $p < .01$), Logical Memory 3rd recall ($F(1, 89) = 13.253$, $p < .001$), and Logical Memory Recognition ($F(1, 89) = 4.500$, $p < .05$). On all of these tasks, younger participants performed significantly better than older participants.

Verbal Free Recall. The results from the multiple regression indicate that in the saccharin condition, age was a significant predictor of Verbal Free Recall performance after step 4 ($R^2 = .237$; $F_{inc}(1,87) = 27.956$, $p < .001$). Specifically, increasing age was associated with decreased performance. In the glucose condition, the multiple regression results indicate that age was a significant predictor of Verbal Free Recall performance after step 4 ($R^2 = .161$; $F_{inc}(1,87) = 19.113$, $p < .01$). The results of the ANOVA indicated that there was a significant main effect of age ($F(1, 89) = 20.366$, $p < .001$). Younger participants performed significantly better than older participants on this task.

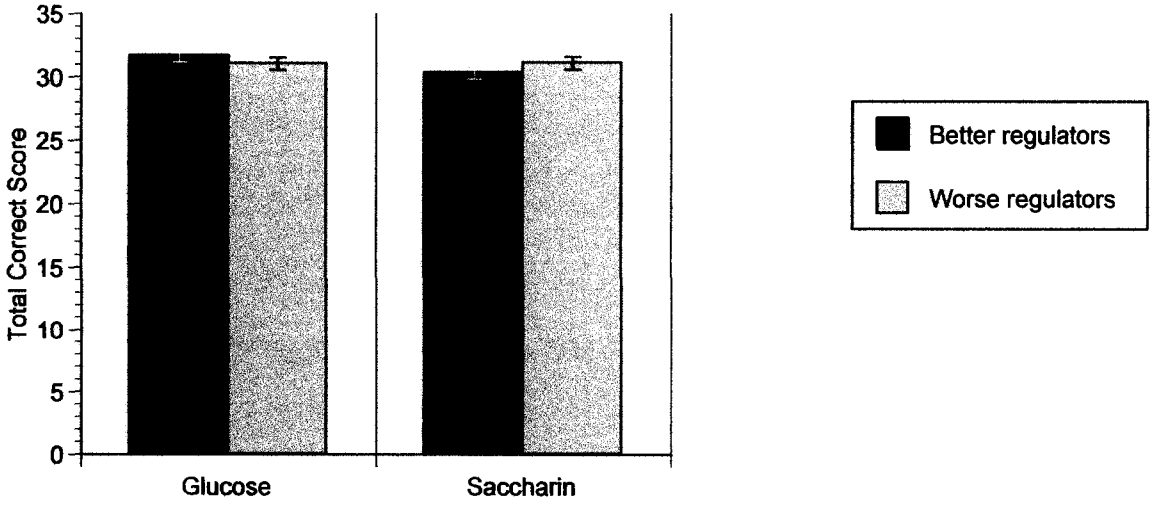
Order Recall. Multiple regression results revealed no significant results. The results of the ANOVA indicated that there was a trend for a main effect of glucose regulation ($F(1, 89) = 3.619$, $p = .06$). Participants with better glucose regulation performed better than those with worse glucose regulation on this task.

Measure of Visuospatial Functioning:

Rey-Osterrieth Complex Figure and Taylor Complex Figure. The results from the multiple regression indicate that in the saccharin condition, age was a significant predictor of Complex Figure immediate recall performance after step 4 ($R^2 = .002$; $F_{inc}(1,88) = 4.040$, $p < .05$), and Complex Figure delayed recall performance after step 4 ($R^2 = .042$; $F_{inc}(1,88) = 7.466$, $p < .01$). In both cases, increasing age was associated with decreased performance. In the glucose condition, the multiple regression results indicate that age was a significant predictor of Complex Figure immediate recall performance after step 4 ($R^2 = .065$; $F_{inc}(1,88) = 8.729$, $p < .01$), and Complex Figure delayed recall performance after step 4 ($R^2 = .114$; $F_{inc}(1,88) = 14.154$, $p < .001$). In both cases, increasing age was associated with decreased performance.

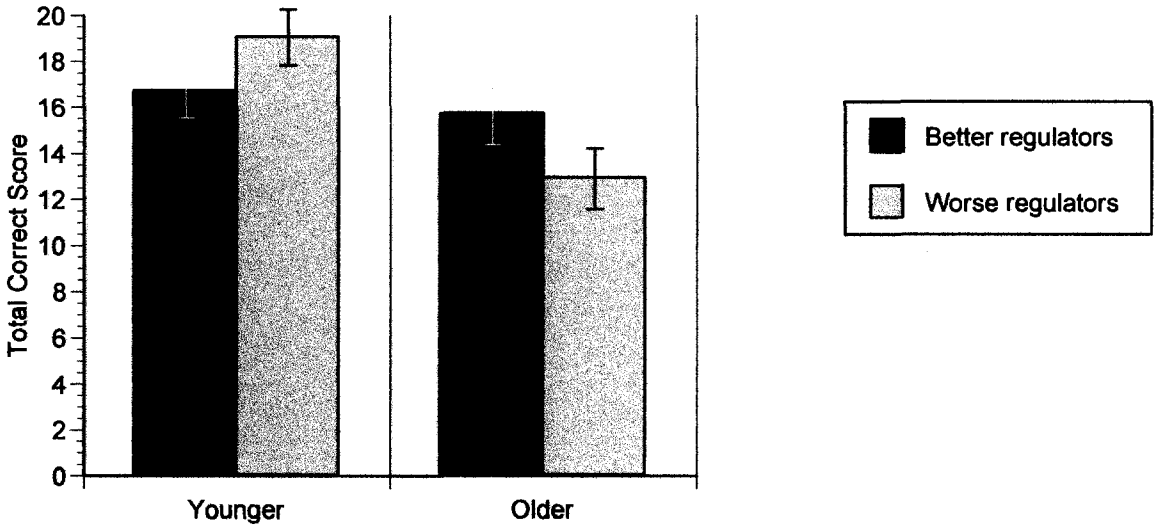
The results of the ANOVA indicated that there was a significant interaction effect of solution by glucose regulation for the Complex Figure copy ($F(1,89) = 4.186$, $p < .05$). Tukey's HSD tests showed that better regulators performed better in the glucose condition than in the saccharin condition. Figure 5 shows the results for the four groups.

Figure 5. Rey Complex Figure Copy Performance



The results of the ANOVA also indicated that there was a significant main effect of age for the Complex Figure immediate recall ($F(1, 89) = 5.273$, $p < .05$). Younger participants performed significantly better than older participants on this task. For the Complex Figure delayed recall, the ANOVA revealed a significant main effect of age ($F(1, 89) = 7.887$, $p < .01$). Again, younger participants performed significantly better than older participants on this task. There was also a significant interaction of age by glucose regulation ($F(1, 89) = 4.152$, $p < .045$) on Complex Figure delayed recall. Tukey's HSD tests showed that younger participants with worse glucose regulation performed better than older participants with worse glucose regulation. Figure 6 shows the results for the 4 groups.

Figure 6. Rey Complex Figure Delayed Recall Performance



Measure of Central Executive Functioning:

Modified Brown-Peterson Task. Performance was at ceiling for participants during the baseline and waiting conditions of the Modified Brown-Peterson task so this data was not further analyzed.

For the counting condition of the Modified Brown-Peterson task, the results from the multiple regression indicate that in the saccharin condition, the glucose component was a significant predictor of performance after step 1 ($R^2 = .075$; $F_{inc}(1,91) = 8.500$, $p < .01$) and age was a significant predictor of performance after step 4 ($R^2 = .158$; $F_{inc}(1,88) = 10.344$, $p < .01$). Specifically, increasing age and worse glucose regulation were associated with decreased performance. For the counting condition of the Modified Brown-Peterson task in the glucose condition, the glucose regulation component was a significant predictor of performance after step 1 ($R^2 = .088$; $F_{inc}(1,91) = 9.842$, $p < .01$) and age was a significant predictor of performance after step 4 ($R^2 = .247$; $F_{inc}(1,88) = 22.011$, $p < .001$). Specifically, increasing age and worse glucose regulation were associated with decreased performance.

The ANOVA showed a significant main effect of age ($F(1, 89) = 20.587$, $p < .001$), and a trend for a main effect of glucose regulation ($F(1, 89) = 2.829$, $p = .096$). Participants with better glucose regulation performed better than those with worse glucose regulation, and younger participants performed significantly better than older participants on this task.

DISCUSSION

The present study investigated the effect of variations in glucose regulation and glucose ingestion on cognitive functioning in a community sample of healthy elderly adults. To the author's knowledge, this is the largest study that has examined cognitive functioning in a healthy elderly sample as a function of glucose regulation. There were four hypotheses postulated at the outset of the study. The first hypothesis was that progressively worse glucose regulation would result in progressively worse performance

on all neuropsychological measures. The second hypothesis stated that increasing age would result in worse performance on all neuropsychological measures. The third hypothesis postulated that poor glucose regulation and increasing age would interact to produce the greatest performance decrements on all neuropsychological measures. Lastly, as per research demonstrating glucose-improvement of memory and other cognitive functions, the fourth hypothesis was that performance on cognitive tasks would be significantly better in the glucose condition relative to the saccharin condition, and that this effect would be more prominent in participants with worse glucose regulation.

Correlational Analysis

Preliminary analysis of the correlations between the biological measures and the results of the cognitive tasks revealed that peak glucose, glucose at 1 hour, evoked glucose (blood glucose at 1 hour – fasting, peak glucose – fasting, and area under the curve (AUC)) were most often correlated with cognitive performance. These findings are consistent with prior investigations that have observed significant correlations between blood glucose values and performance on various cognitive tasks in younger (Craft et al., 1994; Donohue & Benton, 1999; Donohue & Benton, 2000; Messier et al., 1999) and older (Craft et al., 1994; Manning et al., 1990; Messier et al., 1997) adults. In concert with the findings of Kaplan et al. (2000), it was observed that insulin and HOMA indices were also correlated with cognitive measures, although in the present study, correlations were fewer that what was observed for the glucose indices. Cardiovascular risk factors were found to be generally uncorrelated with cognitive task performance with the exception of Logical Memory 1st recall, Order Recall, and Letter-Number Sequencing. Additionally, more correlations were observed in the saccharin condition relative to the

glucose condition, which suggests that the solution ingested modulated the effect of variations in glucose regulation and other biological indices on cognitive performance. The effect of glucose ingestion on cognitive performance will be discussed below.

Cognitive Performance and Glucose Regulation

Firstly however, the question of whether cognitive performance is influenced by variations in glucose regulation will be addressed. Multiple regression analyses and repeated measures ANOVAs were conducted to investigate this relationship. It was observed that progressively worse glucose regulation predicted poorer performance on measures of working memory and executive function (i.e., on the Arithmetic, Digit Span Backward, Letter-Number Sequencing, Spatial Span Forward, Spatial Span Backward (trend), and Modified Brown Peterson (MBP) tasks). The glucose component (obtained from the factor analysis) was most often found to significantly predict cognitive performance. Thus, using this factor, we separated participants into better and worse regulators. We also separated participants into younger (55-72 years) and older (> 72 years) groups. Similar to what was observed in the regression analyses, participants with better glucose regulation performed better on measures of working memory and executive function (i.e., on the Arithmetic, Digit Span Backward, Letter-Number Sequencing, and MBP (trend) tasks), and processing speed (i.e., on the Symbol Search and Digit Symbol Coding (trend) tasks) compared to participants with worse glucose regulation. There was also a trend for better performance by better regulators on one task of verbal memory (i.e., Order Recall).

These findings are in agreement with a number of other studies that have observed that healthy individuals with relatively worse glucose regulation and those with impaired

glucose tolerance tend to perform worse on cognitive measures in comparison to those with better glucose regulation (Craft et al., 1992; Hall et al., 1989; Hiltunen et al., 2001; Kalmijn et al., 1995; Kaplan et al., 2000; Manning et al., 1990; Messier et al., 1997; Vanahanen et al., 1998). These findings are also in concert with investigations that have shown that elderly adults with Type II diabetes generally perform worse on cognitive tasks compared to age-matched controls (Awad et al., 2004; Biessels et al., 2002; Stewart & Liolitsa, 1999; Strachan et al., 1997; Strachan et al., 2002).

Cognitive Performance and Age

As hypothesized, age was an important predictor of cognitive performance. Again, both multiple regression analyses and repeated measures ANOVAs were conducted to investigate this relationship. Increasing age was associated with worse performance on measures of working memory and executive function (i.e., Arithmetic, MBP, Digit Span Backward, Spatial Span Backward, Letter Number Sequencing), processing speed (Digit-Symbol Coding, Symbol Search), verbal memory (i.e., Logical Memory, Verbal Free Recall), and visual memory (i.e., Complex Figure immediate and delayed recall). There relationships were observed in both conditions (glucose and saccharin), with the exception of Spatial Span Backward that was only observed in the glucose condition. Similar to what was observed in the regression analyses, the ANOVA revealed that younger participants performed better than older participants on measures of working memory and executive function (i.e., Arithmetic, MBP (trend), Digit Span Backward (trend), Letter-Number Sequencing, Spatial Span Backward), processing speed (i.e., Symbol Search, Digit Symbol Coding), verbal memory (i.e., Logical Memory,

Verbal Free Recall), and visual memory (i.e., Complex Figure immediate and delayed recall).

These findings showing an association between age and cognitive performance are not surprising, as it is well-established that with age, the brain undergoes structural, biochemical, and electrophysiological changes with resultant declines in various cognitive functions. In particular, the cognitive areas that are typically affected by age include memory (encoding and retrieval, in particular), working memory, psychomotor and cognitive speed, cognitive flexibility, and novel problem-solving (Craik et al., 1995; Lezak, 1995).

Cognitive Performance as a Function of Age by Glucose Regulation

It has been suggested that poor glucose regulation and increasing age interact to produce a greater degree of cognitive impairment (Awad et al., 2004; Ryan & Geckle, 2000). In the present study, repeated measures ANOVAs were conducted in order to examine the interaction between age and glucose regulation and in particular, to determine if the older participants with worse glucose regulation would evidence the poorest performance on the cognitive measures) relative to other three groups (i.e., older participants with better glucose regulation, younger participants with better glucose regulation, and younger participants with worse In general, relative to the other three groups, it was observed that the older participants with worse glucose regulation obtained the lowest scores on the majority of cognitive measures glucose regulation). (i.e., on the Arithmetic, Digit Symbol Coding, MBP, Digit Span Backward, Symbol Search, Spatial Span Forward, Spatial Span Backward, Logical Memory, Complex Figure immediate recall, Complex Figure delayed recall, Letter-Number Sequencing, Verbal Free Recall,

and Order Recall tasks), but only a few significant findings were observed. Specifically, it was demonstrated that older participants with worse glucose regulation performed significantly more poorly than the other three groups on a task of working memory (i.e., Arithmetic). Similarly, older participants with worse glucose regulation performed significantly more poorly on a visual memory task (i.e., Complex Figure delayed recall) compared to younger participants with worse glucose regulation. There was also a trend for younger participants with better glucose regulation to perform better than the other three groups on a working memory task (i.e., Letter-Number Sequencing).

Cognitive Performance and Glucose Ingestion

The improvement of memory and other cognitive functions with the ingestion of glucose has been observed in number of studies (e.g., Allen et al., 1996; Craft et al., 1994; Gonder-Frederick et al., 1987; Hall et al., 1989; Kaplan et al., 2000; Manning et al., 1998; Manning et al., 1992; Manning et al., 1990; Manning et al., 1997; Messier et al., 1997; 1999; Parsons & Gold, 1992). Studies have also shown that glucose appears to have a stronger effect on functions mediated by the medial temporal lobe, including the hippocampus, such as verbal episodic memory (Craft et al., 1992; Craft et al., 1994; Gonder-Frederick et al., 1987; Manning et al., 1990; Manning et al., 1992; Manning et al., 1997; Parsons & Gold, 1992), than those mediated by other brain regions such as working memory (Craft et al., 1992; Craft et al., 1994; Manning et al., 1990), procedural memory (Craft et al., 1994; Foster, Lidder, & Sunram, 1998; Manning et al., 1990), or response inhibition (Benton, Owens, & Parker, 1994; Craft et al., 1994). Additionally, a few studies have reported that individuals with poor glucose regulation may be more sensitive to the cognition-enhancing effects of glucose than are individual with better

regulation (Kaplan et al., 2000; Messier & Gagnon, 1996). As indicated above, in the present study, it was observed that the majority of correlations between biological indices of glucose regulation and cognitive performance occurred in saccharin condition. As per the correlations, the prediction of progressively worse performance on cognitive tasks by progressively worse glucose regulation (as discussed above) was observed more frequently when participants had ingested saccharin (i.e., on the Arithmetic, MBP, Digit Span Backward, Spatial Span Forward, Spatial Span Backward (trend), and Letter-Number Sequencing tasks) relative to the when they had ingested glucose (i.e., on the Arithmetic and MBP tasks), which suggests that glucose modulated the relationship between glucose regulation and cognitive function.

The impact of solution as a function of age and glucose regulation was examined with the repeated measures ANOVA analysis. In general, there were few significant findings. On a visual spatial task (i.e., Complex Figure copy), participants with better glucose regulation in the saccharin condition performed significantly better than participants with better glucose regulation in the glucose condition. Thus, glucose appeared to decrease performance among better regulators on this task. On a task of working memory (i.e., Digit Span Backward), there was a trend for participants with worse glucose regulation in the saccharin condition to perform significantly more poorly than participants with better glucose regulation in the glucose condition. On a task of processing speed (i.e, Symbol Search), a more complex interaction was observed. In general, younger participants with better glucose regulation performed the best on this task after having ingested glucose relative to the other groups. Additionally, after ingesting glucose, older participants with worse glucose regulation performed more

poorly than younger participants (better and worse regulators) in the saccharin condition; after ingesting saccharin, they performed more poorly than younger participants with worse glucose regulation in the glucose condition.

Thus, in general, the findings from the present study suggest that both age and glucose regulation significantly impact cognitive functioning. However, in contrast to previous investigations, a significant enhancement of cognitive performance by glucose was not clearly observed. These findings will be further addressed below.

Glucose Regulation and Specificity of Cognitive Domains

Interestingly, we did not find a strong relationship between poor glucose regulation and poor performance on tasks of verbal declarative memory, as has been previously reported in older adults with worse glucose regulation (Convit et al., 2003; Kaplan et al., 2000), adults with impaired glucose tolerance (Vanhanen et al., 1997; Vanhanen et al., 1998), and in older adults with Type II diabetes (Awad et al., 2004; Biessels et al., 2001; Stewart & Liolitsa, 1999; Strachan et al., 1997; Strachan et al., 2002). It is unclear why verbal declarative memory tasks were generally unaffected by variations in glucose regulation in the present investigation. However, while verbal memory is one area that has been shown to be most consistently affected by Type II diabetes, it is important to note that a large number of studies have not observed significant findings on such tasks. Specifically, in their recent review of Type II diabetes and cognitive function, Awad et al. (2004) reported that only 3 of 12 population-based studies and 15 of 43 studies reported verbal memory deficits, which suggests that verbal memory deficiencies in this population are variable.

In the present study, participants with worse glucose regulation had poorer performance than participants with better glucose regulation on measures of working memory, executive function, and processing speed. These findings are in agreement with other investigations that have reported deficits on measures of attention (Vanhanen et al., 1997), executive function (Kaplan et al., 2000; Vanhanen et al., 1997) and processing speed (Kaplan et al., 2000; Vanhanen et al., 1997) in healthy older adults with poorer glucose regulation and individuals with impaired glucose tolerance. They are also in line with numerous studies reporting deficits in attention (Dey et al., 1997; Jagusch et al., 1992; Manschot, Brands, van der Grond, Kessels, Algra, Kappelle, & Biessels, 2006; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990), executive function and working memory (Desmond et al., 1993; Gregg et al., 2000; Lowe, Tranel, Wallace, & Welty, 1994; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Manschot et al., 2006; Reaven et al., 1990; Ryan & Geckle, 2000b; van Boxtel et al., 1998; Wahlin et al., 2002), and processing speed (Gregg et al., 2000; Jagusch et al., 1992; Manschot et al., 2006; Meuter, Thomas, Gruneklee, Gries, & Lohman, 1980; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; Reaven et al., 1990; Ryan & Geckle, 2000b; U'Ren et al., 1990; van Boxtel et al., 1998; Vanhanen et al., 1997; Vanhanen et al., 1999) in younger and older adults with Type II diabetes.

The cognitive areas that were negatively affected by relatively worse glucose regulation (i.e., working memory, executive function, processing speed) in the present study are those that are typically affected by subcortical and white matter changes (Breteler, van Amerongen, van Swieten, Claus, Grobbee, & van Gijn, 1994a; DeCarli, Murphy, Tranh, Grady, Haxby, & Gillette, 1995; Erkinjuntti & Hachinski, 1993;

Gunning-Dixon & Raz, 2003; Nordahl, Ranganath, Yonelinas, DeCarli, Reed, & Jagust, 2005). The pathology of white matter changes is non-specific and includes multiple types of injury such as a reduction in myelination of axons, narrowing of small vessels, and gliosis (see Bronge, 2002, for review). Among other small vessel cerebrovascular disease risk factors (i.e., hypertension, prior stroke), glucose intolerance and hyperinsulinemia (Feskens & Kromhout, 1992; Juhan-Vague et al., 1993; Fontbonne, Charles, Thibult, Richard, Claude, Warnet, Rosselin, & Eschwege, 1991) and Type II diabetes (Breteler, van Swieten, Bots, Grobbee, Claus, & van den Hout, 1994b; DeCarli et al., 1995) have been shown to be associated with white matter disease. In a recent investigation, Manschot et al. (2006) found that Type II diabetes was associated with deep white matter lesions, cortical and subcortical atrophy, infarcts (silent) and impaired cognitive function (i.e., attention, executive function, processing speed, and memory). It was also observed that cognitive function was inversely related to white matter lesions, atrophy, and the presence of infarcts, in addition to a modest association with HBA_{1c} and diabetes duration. Although our participants were generally healthy non-diabetics, we did not measure the degree of white matter disease or the degree of subcortical or cortical atrophy. Thus, we cannot exclude these mechanisms in explaining the apparent association between poor glucose regulation and cognitive impairment in the present study. Additionally, participants with worse glucose regulation tended to have higher insulin measures and there was strong association between insulin measures and several cardiovascular risk factors (i.e., HDL cholesterol and BMI), which lends further credence to a vascular profile.

Insulin Sensitivity

While the glucose component from the factor analysis (comprised of mainly of evoked glucose level indices) appeared to be the most highly associated with performance on cognitive measures, HOMA and insulin indices were less so. However, as indicated above, it was observed that older participants with worse glucose regulation had significantly higher 2-hour insulin values compared to participants with better glucose regulation (older and younger), and that younger participants with worse glucose regulation had significantly higher 2-hour insulin values than younger participants with better regulation. There was also a trend for lower insulin resistance values in younger participants with better glucose regulation compared to older participants with worse glucose regulation and a tendency for participants with worse glucose regulation to have higher fasting and 1-hour insulin levels than participants with better glucose regulation. Therefore, we cannot rule out the possibility that the glucoregulatory effects on cognition noted in the present study were mediated in part, by insulin sensitivity. Additionally, it is important to note that we measured insulin on only one occasion and we did not obtain cerebrospinal insulin levels, which have been shown to be more predictive of the association between insulin and cognitive functions (Craft, Asthana, Schellenberg, Baker, Cherrier, Boyt, Martins, Raskind, Peskind, & Plymate, 2000; Craft, Asthana, Schellenberg, Cherrier, Baker, Newcomer, Plymate, Latendresse, Petrova, Raskind, Peskind, Lofgreen, & Grimwood, 1999; Craft, Peskind, Schwartz, Schellenberg, Raskind, & Porte, 1998)).

The Impact of Fasting Glucose

In reaching the conclusion that worse glucose regulation negatively affected cognitive performance in our sample, the impact of fasting glucose on cognitive function

must also be addressed. We measured blood glucose levels at baseline (before beginning cognitive testing) and 60 minutes after we began the testing session. The average value at 60 minutes after beginning the testing session was 5.5 mmol/l (during the saccharin session). This value is far from the 3.0 mmol/l level where hypoglycemia would begin to produce cognitive impairments (Boyle, Nagy, O'Connor, Kempers, Yeo, & Qualls, 1994; Gold, Deary, MacLeod, Thomson, & Frier, 1995; Kerr, Reza, Smith, & Leatherdale, 1991). Additionally, none of the participants had baseline glucose levels below 4.0 mmol/l and no participant had blood glucose levels below 4.4 mmol/l 60 minutes after cognitive testing began. Overall, less than 10% of subjects had blood glucose levels less than 5.0 mmol/l on those 2 occasions. These results indicate that it is unlikely that the poorer performance on cognitive tasks as a function of glucose regulation could be attributed to a hypoglycemic effect during the saccharin condition. The lack of an effect of glucose on cognitive functioning in the present study also supports this assertion.

The Impact of Age

We also examined the suggestion that the deleterious effect of poorer glucose regulation is more apparent in older participants than in younger ones. In a review on cognitive deficits in Type II diabetes, Ryan and Geckle (2000a) recently suggested that diabetes is only one of many factors that results in decreased cognitive functioning in aging, and that the impact of diabetes is more easily observed in older participants whom are also more likely to have other brain pathology such as cerebrovascular disease. The present results are in general agreement with this view such that there older participants with worse glucose regulation tended to perform the poorest on most neuropsychological measures. Despite this, there were fewer significant findings than expected. This may be

due to the fact that our sample was older (i.e, mean age 70, median age 72) and thus, the age difference between our 'younger' (mean age 64) and 'older' (mean age 77) groups may not have been large enough to detect significant differences.

The Impact of Glucose Ingestion

There are several factors that could potentially explain the lack of a clear effect of glucose in the present study. The first factor is the amount of glucose ingested. The present study utilized a 50g dose, which has been successfully used in previous investigations with older adults. However, other studies have found a memory-improving effect from 25g (Foster et al., 1998; Kennedy & Scholey, 2000) to 75g (Manning, Ragozzino, & Gold, 1993) of glucose. Messier, Pierre, Desrochers, and Gravel (1998) and Parsons and Gold (1992) have also demonstrated a dose-response curve for glucose improvement of memory, which indicates that a different dose of glucose in the present study may have led to the observation of glucose-related cognitive improvement.

Another factor that has been reported to influence the likelihood of observing a memory-enhancing effect of glucose is task difficulty (Kaplan et al., 2000). Performance on more difficult tasks that involve interference are generally more likely to show improvements following glucose ingestion (Scholey, Harper, & Kennedy, 2001; Sumram-Lea, Foster, Durlach, & Perez, 2002). The only task that involved interference in the present study was the MBP, which required participants to recall three consonant letters after a 20 second serial subtraction task. However, we did not observe any glucose facilitation on this task. It is possible that glucose ingestion may not have an important influence on complex working memory even though participants with worse regulation tended to perform more poorly on this task.

Placebo expectancy effects have also been shown to increase the size of the memory-improving effect of glucose (Green, Taylor, Elliman, & Rhodes, 2001). In the present experiment, 63% of participants correctly identified the drink they received on their second visit (chance levels would be 50%) suggesting that most participants were blind to the nature of the drink they ingested. Thus expectancy effects were minimized possibly resulting in a decreased effect of glucose enhancement of cognition.

Another possible factor that may have influenced the likelihood of observing an improving effect of glucose is the timing of cognitive tasks with the rise in blood glucose level, as it has been suggested memory-improvement is observed when glucose levels reach a certain level. Messier et al. (1998) observed that glucose levels begin to increase at approximately 5 minutes after glucose ingestion and reach a peak between 30 minutes to one hour. The most prominent effects of glucose on performance were observed around 15-25 minutes after the ingestion of glucose. In the present study, the tests occurring 15-25 minutes after ingestion were Digit Symbol-Coding and MBP, neither of which showed an effect of glucose ingestion. Thus, in the present study, we could not find a time-dependent pattern that would suggest that blood glucose levels following the ingestion of glucose had a specific impact on performance.

There are several limitations to the present study. The sample was comprised of older adults (55 years and older) who were randomly selected on the basis of strict exclusionary criteria. Thus, the findings are limited in generalizability to relatively healthy older adults. Also, the sample consisted mainly of female participants, which also limits generalizability. Lastly, the estimates of glucose regulation were not the gold standard (i.e., we did not use a hyperglycemic clamp).

Importantly however, the present study has several strengths. It was very well controlled, utilized a wide range of standardized cognitive tests, and also included well-controlled non-standardized tests. It is one of the largest studies examining cognitive functioning as a function glucose regulation in healthy older adults. It provides strong evidence to suggest that the development of cognitive difficulties in aging is associated with worsening glucose regulation, independent of overt IGT or Type II diabetes. The strict exclusion criteria support the notion that the decrements observed in the participants with poorer glucose regulation were unlikely to be attributable to other conditions (e.g., depression, stroke). Given that the participants were generally healthy and evidenced a high level of education, the extent of these deficits as outlined in the in present study may be underestimated in the general population.

Given that several studies have observed gender difference between men and women in glucose regulation (Paula, Pimenta, Saad, Paccola, & Piccinato, 1990) and in terms of sensitivity to glucose enhancement of memory (Craft et al., 1994), future research in this area should aim at comparing males and females on cognitive tasks as a function of glucose regulation to see if any differences would emerge. Including brain imaging in future studies would also be important to see if any structural or functional differences can be observed as a function of varying levels of glucose regulation and cognitive function. Finally, it would be important for future research to focus on methods of preventing the development of impaired glucose regulation and other typically co-morbid difficulties (e.g., cardiovascular risk factors), as they are highly associated with poor lifestyle choices (e.g., poor diet, lack of physical exercise) and therefore, modifiable.

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APPENDIX

Table 1. Studies Evaluating Neuropsychological Effects of Type 2 Diabetes.

Reference	Year	Diabetes (n;% males)	Diabetes: Age (yrs)	Diabetes: Educ (yrs or %)	Controls (n; % males)	Controls: Age (yrs)	Controls: Educ (yrs or %)
Cross-Sectional Studies							
Assisi et al.	1996	12	61	8.9	17	62	8.7
Atiea et al.	1995	20 (70%)	69		20 (65%)	68	
Cerizza et al.	1993	20 (25%)	73		20 (30%)	72	
Cosway et al.	2001	38 (42%)	58	11.2	38 (39%)	56	11.8
Dey et al.	1997	28 (64%)	47	12	28 (50%)	48	11.6
Helkala et al.	1995	20 (65%)	66		22 (64%)	65	
Jagusch et al.	1992	26 (23%)	65		13 (8%)	71	
Lowe et al.	1994	80 (25%)	59	46.3% > HS	81(47%)	55	58% > HS
Mattlar et al.	1985	33 (67%)	56	88% > ES	33 (67%)	55	97% > ES
Meuter et al.	1980	35 (46%)	57	60%=ES: 23%=MS: 17%=HS	35 (46%)	56	60%=ES: 23%=MS: 17%=HS
Mooradian et al.	1988	43 (100%)	66		41 (100%)	65	
Motta et al.	1996	23 (65%)	74		30 (50%)	73	
Perlmuter et al.+	1984	140 (54%)	64	11.7	38 (43%)	63	12.5
Perlmuter et al.+	1987	86	60	12.3	25	60	12
Reaven et al.	1990	29 (66%)	69	14.7	30 (53%)	68	15
Ryan et al.	2000	50 (30%)	51	14.4	50 (24%)	51	14
Sinclair et al.	1997	109	83		106	83	
Soininen et al.	1992	12 (0%)	78		59 (34%)	74	
Tun et al.+	1987	70	60	12.9	16	60	12.9
U'ren et al.	1990	19 (16%)	70	12	19 (16%)	71	14
Vanhanen et al.	1997	35 (37%)	67	7.2	26 (38%)	63	7.8
Wahlin et al.	2002	31 (7%)	85	8.4	307 (20%)	85	8.7
Worrall et al.	1993	90 (32%)	68	7	90 (32%)	68	8
Zaslavsky et al.	1995	29 (48%)	60	7.6	34 (29%)	59	6.9

Note. CO: College: ES: Elementary school: HS: High school: MS: Middle school; ~: Mean age of entire sample; +: Common subjects in more than one study.

Table 1. *(continued).*

Reference	Year	Diabetes (n;% males)	Diabetes: Age (yrs)	Diabetes: Educ (yrs or %)	Controls (n; % males)	Controls: Age (yrs)	Controls: Educ (yrs or %)
Population Studies							
Amato et al.	1996	197 (32%)	74		1142 (44%)	74	
Croxson et al.	1995	33 (47%)	>75		187 (55%)	>75	
Desmond et al.	1993	29	70	10.2	220	71	12.6
Elias et al.	1997	187 (50%)	69		1624 (40%)	67	
Grodstein et al.	2001	82 (0%)	74	HS + 3.5	2292 (0%)	74	HS + 4
Hiltunen et al.	2001	98 (32%)	>70		281 IGT+ NGT	>70	
Kilander et al.	1997	68	~72		425	~72	
Launer et al.	1993	354	65-84	27% > HS	3617	65-84	20% > HS
Lindeman et al.	2001	188	73	10.9	476	74	12.3
Mangione et al.	1993	33	>62		436	>62	
Scherr et al.	1988	347-584	>65		1830-3079	>65	51%=ES: 43%=HS: 6%=CO
Scott et al.	1998	178 (51%)	72	74% = CO	953 (43%)	68	68% = CO
van Boxtel et al.	1998	35	70		1325	24-81	
Vanhanen et al.	1999	183 (35%)	73	5.9	732 (34%)	73	6.9
Woo et al.	1994		>70		2011 (49%)	>70	

Note. CO: College; ES: Elementary school; HS: High school; MS: Middle school; ~: Mean age of entire sample; +: Common subjects in more than one study.

(continued)

Table 1. *(continued).*

Reference	D Duration (yrs)	Treatment Modality(%)	HbA1 (%)	FG (mmol/L)	Neurological	Psychiatric	Depressive Sx	Medication**	Substance Abuse	BP	CVD	Cog/ Educ
Cross-Sectional Studies												
Assisi	11			8.5			X	X		M		M
Atiea	10	D:15% /O:70% /I:15%	10.6		X		sX, M	X		D>C	X	M
Cerizza	14	D:55% /I:45%	9.9c	10	X			X			X	
Cosway	6	D: 21% /O: 53% / I:16% /O+I: 16%	7.6c		X	X	M	X	X, Ma,cg	sX,M	X	M
Dey	8	D: 17% /O: 82%	8.0c	6.1	X	X		X	X	M	X	M
Helkala	10	D: 20%/ O: 55%/ I: 25%	8.6c	11.7			M		Ma,cg	D>C	X	
Jagusch	12	O:12%/ I: 46%/ I+ O:42%	10.3	10.1	X				X	sX	X	
Lowe	7		8.1		X	X	D>C		Ma	D>C	D>C	M
Mattlar	7		9.3		X	X		X	X	X		
Meuter	8	D: 9%/O: 91%		11								M
Mooradian	13	I: 47%/O:53%	10.9	10	X	X		X	X	M	X	
Motta	6				X		M					
Perlmuter +		D:36% /O:24% /I:40%	8.8c		X	X	M		X	M	X	M
Perlmuter +						X		X	X		X	M
Reaven			11.0c	11.3	X		X		X		X	M
Ryan	8	D:18%; O:56%; I: 26%	10.2		X	X	M		X, Mcg	D>C		M
Sinclair	8	D: 36%; O: 50%; 14%	9.4							M	M	
Soininen	9	O:92%/ I:1%		6.1	X					sX, M		
Tun +							D>C	X	X		X	M
U'ren	12	D: 16%/O: 14% / I:60%/O+I: 16%	11.4		X			X	X	M	X	M
Vanhanen				9.3	X	X	M		Ma,cg	D>C		M

Note. BP: Blood Pressure; C: Control subjects; D: Diabetic subjects; Cog/Educ: Premorbid cognitive/education matching; CVD: Cardiovascular/cerebrovascular risk factors: E: evaluated FG: Fasting Glucose of Diabetes sample; M: matched or controlled statistically; Substance abuse= s: serious; a: alcohol; cg: cigarette; Treatment Modality= D: Diet; O: Oral hypoglycaemic; I: insulin; X: exclusion criteria; **: Psychoactive Medication; +: common subjects in more than one study.

Table 1. *(continued)*.

Reference	D Duration (yrs)	Treatment Modality(%)	HbA1 (%)	FG (mmol/L)	Neurological	Psychiatric	Depressive Sx	Medication**	Substance Abuse	BP	CVD	Cog/ Educ
Wahlin		O: 39%; I: 6%			X	X					D>C	M
Worrall	8	D:24%/O: 68%			X		X	X	D<Ca	M	D>C	D<C
Zaslavsky	8	D: 3%/O: 69%/I: 28%	8.6c	9	X	X	X		X		X	M
Population Studies							D>C					
Amato												
Croxson												
Desmond											X	
Elias	0-29	I:6%							Ma,cg	D>C: M	D>C: M	M
Grodstein	12	O: 71%/I: 38%					M		Mcg	D>C: M	X	D<C: M
Hiltunen							M		Ma		M	M
Kilander												M
Launer												M
Lindeman							D>C					D<C: M
Mangione												M
Scherr												M
Scott							D>C: M			D>C: M		M
van Boxtel					X			X			sX	
Vanhanen			7.4	8.8	X		M		D<Cs, Ma	D>C	D>C	D<C: M
Woo												

Note. BP: Blood Pressure; C: Control subjects; D: Diabetic subjects; Cog/Educ: Premorbid cognitive/education matching; CVD: Cardiovascular/cerebrovascular risk factors; E: evaluated FG: Fasting Glucose of Diabetes sample; M: matched or controlled statistically; Substance abuse= s: serious; a: alcohol; cg: cigarette; Treatment Modality= D: Diet; O: Oral hypoglycaemic; I: insulin; X: exclusion criteria; **: Psychoactive Medication; +: common subjects in more than one study.

(continued)

Table 1. *(continued)*.

Reference	Overall Cognition	Cognitive Screening	Memory	Paragraph Imm	Paragraph Del	Verbal Imm	Verbal Del	Verbal Rec	Nonverbal Imm	Nonverbal Del
Cross-Sectional Studies										
Assisi		0.14				-0.3	-0.6		-0.06	
Atiea	0.42			0.12	-0.12				0.32	
Cerizza	0.58									
Cosway				-0.18	-0.02	0.32;0.05	0.25; 0.08		0.1	0.28
Dey		1.34	E*							
Helkala						0.86*	0.91*	0.12	0.36;0.50	0.2
Jagusch				E		E*; E*			E*	
Lowe		0.17		0.05	0.15	0.06	0.1	0.07	-0.2	
Mattlar				0	0	-0.21; 0.06	-0.26; 0.32	-0.11; 0.29	0.09	
Meuter			0.63							
Mooradian						0.52*		0.3	0.51*	
Motta		0.24								
Perlmuter +						0.65*				
Perlmuter +						0.49*				
Reaven						1.07*				
Ryan				-0.36*	-0.33	0.41	0.2		0.12	0.18*
Sinclair		E*								
Soininen			0.46							
Tun + U'ren				1.25*	1.16*	0.73*				
Vanhanen		0.66				0.61*	0.34		0.87*	0.71
Wahlin						E*				
Worrall		0.36*					0.37*			
Zaslavsky						E	E		E	E

Table 1. (*continued*).

Reference	Overall Cognition	Cognitive Screening	Memory	Paragraph Imm	Paragraph Del	Verbal Imm	Verbal Del	Verbal Rec	Nonverbal Imm	Nonverbal Del
Population Studies										
Amato		0.19*								
Croxson		OR: 3.38* <24 MMSE								
Desmond						E				
Elias				OR: 1.36 <25%ile	OR: 1.49* <25%ile	OR: 0.99 <25%ile				
Grodstein		0.24*		0.17	0.26					
Hiltunen		1.2 ≤23 on MMSE								
Kilander		E				E			E	
Launer		OR:1.6* = 22-25 MMSE								
Lindeman		0						0		
Mangione		E*								
Scherr		E			E	E				
Scott		E				E*			E	E
van Boxtel						E*				
Vanhanen						0.07			0.03	0.03
Woo		OR: 0.92 ≤ 7 CAPE								

Note. E: evaluated; Imm: Immediate; Del: Delay; OR: Odds ratio for given score; *statistically significant $p < .05$; +: common subjects in more than one study.

(*continued*)

Table 1. (*continued*).

Reference	Digit Span	Digit Span F	Digit Span B	Spatial Span	Spatial Span F	Spatial Span B	Arithmetic	Visuospatial	Digit Symbol	Processing Speed	Trails A	Stroop x
Cross-Sectional Studies												
Assisi		-0.35	-0.54		-0.52	0.78		-0.1				
Atiea		0.8	0.47				-0.5		0.03	0.17		
Cerizza	0.54						-0.08	0.51; 0.55; 0.33	0.42			
Cosway								0.1		0.3		
Dey	E*						E	E				
Helkala		0.33	0.09		0	0.38		-0.07;0.69			0.29	
Jagusch	E*			E						E*;E	E*	
Lowe		-0.14	0.04					0.16				
Mattlar	-0.51						-0.38	0.11; 0; 0.16; 0.13	0.13		0	-0.08
Meuter								-0.13		0.61*		
Mooradian		0.19	-0.08									
Motta												
Perlmuter +		0.27	0.37									
Perlmuter +		0	0.19						0.37*			
Reaven	-0.3							0.26	0.86*		0.67*	
Ryan								0.27; 0.39; 0.34	0.41	0.5*		
Sinclair												
Soininen												
Tun +										E		
U'ren		0.34*	0.09				0.64*; 1.34*		0.45	0.34; 0.58*		
Vanhanen		0.42	0.4					0.62	1.2*			1.25*
Wahlin												
Worrall												
Zaslavsky		E										

Table 1. *(continued)*.

Reference	Digit Span	Digit Span F	Digit Span B	Spatial Span	Spatial Span F	Spatial Span B	Arithmetic	Visuospatial	Digit Symbol	Processing Speed	Trails A	Stroop x
Population Studies												
Amato												
Croxson												
Desmond								OR: 3.5* <mean		E		
Elias		OR: 1.22 <25%ile	OR: 1.08 <25%ile									
Grodstein												
Hiltunen												
Kilander		E	E		E	E		E			E; E; E	
Launer												
Lindeman		0.16					0.08				0.02	
Mangione												
Scherr		E										
Scott								E				
van Boxtel									E*			
Vanhanen								0			0.37*; 0.31*	
Woo												

Note. E: evaluated; F: Forward; B: Backward; OR: Odds ratio for given score; *statistically significant $p < .05$; +: common subjects in more than one study.

(continued)

Table 1. (*continued*).

Reference	Fluency-Letters	Fluency-Category	Abstract concept.	Reasoning	WCS	Trails B	Stroop interference	Working Memory	Long-term/ Semantic	Language
Cross-Sectional Studies										
Assisi										
Atiea	0.64							0.43		
Cerizza			0.54	0.58; 0.58					0.62*; 0.40	
Cosway	0.3									
Dey			E	E						E*, E, E
Helkala	0.26	0.31				0.54				
Jagusch										
Lowe	0.46*		0.42*							
Mattlar			0.08	0.06; 0		-0.06	-0.2		-0.19; -0.27	
Meuter										
Mooradian										
Motta										
Perlmuter +									0.31	
Perlmuter +	0.27								0.06	
Reaven					0.95*	0.69*			-0.16	
Ryan						0.31	0.73*	0.34		
Sinclair										
Soininen									0.11;0.07	0.08; 0.37
Tun +										
U'ren	0.31								1.37*	
Vanhanen		0.57					0.83			
Wahlin	E*	E								
Worrall										
Zaslavsky									E	

Table 1. *(continued)*.

Reference	Fluency-Letters	Fluency-Category	Abstract concept.	Reasoning	WCS	Trails B	Stroop interference	Working Memory	Long-term/ Semantic	Language
Population Studies										
Amato										
Croxson										
Desmond			OR:10.9* < mean							E
Elias	OR: 1.23< 25th%ile		OR:1.45< 25th%ile							
Grodstein		0.23								
Hiltunen										
Kilander	E					E			E	
Launer										
Lindeman						0.09				
Mangione										
Scherr										
Scott		E				E				
van Boxtel	E					E*				
Vanhanen	0.24	0.11								
Woo										

Note. E: evaluated; OR: Odds ratio for given score; WCS: Wisconsin Card Sorting; *statistically significant $p < .05$; +: common subjects in more than one study.

(continued)

Table 2. Summary of Studies Evaluating Neuropsychological Effects of Type 2 Diabetes.

Reference	Year	Cognitive Screening	Verbal Memory	Nonverbal Memory	Attention	Visuospatial	Processing Speed	Executive Function	Long-term/ Semantic
Cross-Sectional Studies									
Assisi et al.	1996	E		E	E,E,E,E	E			
Atiea et al.	1995		E,E	E	E,E,E		E,E	E,E	E
Cerizza et al.	1990				E,E	E,E,E	E	E,E,E	E*,E
Cosway et al.	2001		E,E,E,E,E,E	E,E		E	E	E	
Dey et al.	1997	E			E*,E	E		E,E	E*, E, E
Helkala et al.	1995		E*,E*,E	E,E,E	E,E,E,E	E,E	E	E,E,E	
Jagusch et al.	1992		E*,E*,E	E*	E*,E		E*,E*,E		
Lowe et al.	1994	E	E,E,E,E,E	E	E,E	E		E*,E*	
Mattlar et al.	1985		E,E,E,E,E,E	E,E,E	E,E	E,E,E,E	E,E,E	E,E,E,E,E	E,E
Meuter et al.	1980					E	E*		
Mooradian et al.	1988		E*,E	E*	E,E				
Motta et al.	1996	E							
Perlmuter et al.+ 1984	1984		E*		E,E				E
Perlmuter et al.+ 1987	1987		E*		E,E		E*	E	E
Reaven et al.	1990		E*		E	E	E*,E*	E*,E*	E
Ryan et al.	2000		E*,E,E,E	E,E*		E,E,E	E*,E	E*,E,E	
Sinclair et al.	1997	E*							
Soininen et al.	1992								E,E,E,E
Tun et al.+	1987						E		
U'ren et al.	1990		E*,E*,E*		E*,E*,E*,E		E*,E,E	E	E*
Vanhanen et al. 1997	1997	E	E*,E	E*,E	E,E	E	E*,E*	E,E	
Wahlin et al.	2002		E*					E*,E	
Worrall et al.	1993	E*	E*						
Zaslavsky et al.	1995		E,E	E,E	E				E
SD/ NSD	0/4	2/7	15/43	4/19	5/35	0/19	10/22	6/29	3/17

Table 2. (*continued*).

Reference	Year	Cognitive Screening	Verbal Memory	Nonverbal Memory	Attention	Visuospatial	Processing Speed	Executive Function	Long-term/ Semantic
Population Studies									
Amato et al.	1996	E*							
Croxson et al.	1995	E*							
Desmond et al.	1993		E			E*	E	E*	E
Elias et al.	1997		E*,E,E		E,E			E,E	
Grodstein et al.	2001	E*	E,E					E	
Hiltunen et al.	2001	E							
Kilander et al.	1997	E	E	E	E,E,E,E	E	E,E,E	E,E	E
Launer et al.	1993	E*							
Lindeman et al.	2001	E		E	E	E	E	E	
Mangione et al.	1993	E*							
Scherr et al.	1988	E	E,E		E				
Scott et al.	1998	E	E*	E,E	E	E		E,E	
van Boxtel et al.	1998		E*				E*	E*,E	
Vanhanen et al. 1999	1999		E	E,E		E	E*,E*	E,E	
Woo et al.	1994	E							
SD/ NSD		5/11	3/12	0/6	0/9	1/5	3/8	2/13	0/2

Note. SD: Statistically significant difference on at least one measure evaluated in the study; NSD: Statistically Nonsignificant Difference; E: Evaluated; *Significant Difference $p < .05$.

Université d'Ottawa · University of Ottawa

Cabinet du vice-recteur à la recherche
Office of the Vice-Rector, Research

COMITÉ D'ÉTHIQUE DE LA RECHERCHE EN SCIENCES DE LA SANTÉ ET SCIENCE

ATTESTATION D'APPROBATION DÉONTOLOGIQUE

La présente attestation certifie que le Comité d'éthique de la recherche en sciences de la santé et sciences de l'Université d'Ottawa a examiné la demande d'approbation déontologique présentée par Claude Messier pour des modifications à son projet de recherche Effects of glucoregulation on cognitive function (Dossier H04-00-B). Le Comité d'éthique a déterminé que la demande respectait les principes déontologiques établis par l'Énoncé de politique des trois conseils et par les règles de procédure des Comité d'éthique de l'Université d'Ottawa. Le Comité d'éthique a donc accordé une catégorie Ia (Approbation) pour les modifications au projet de recherche. La présente attestation est valide un an à partir de la date indiquée ci-dessous.

Le 12 juin 2000
Date

Lise Frigault
Responsable de la déontologie en recherche
pour la présidente du CÉR en sciences sociales et humanité
Valerie Whiffen

DOSSIER: H04-00-B

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EFFECT OF GLUCOREGULATION ON COGNITIVE FUNCTION

Test Administration Instructions

Table of Contents

General Reminders

(1) Write the subject number on each page of all tests. Code each page with the subject number, session number, and the form (A or B). Label forms clearly.

(2) Before a subject comes in, mark whether you are doing Form A or Form B Arithmetic with a Post-It flag so that you will not make an error while testing.

(3) Code the forms with your experimenter number:

Maria: 1

Nesrine: 2

Cosette: 3

(4) Keep track of the time when testing and ensure that you measure blood glucose 60 minutes after the subject drinks the sweet solution.

(5) Never say "good" or "great" after an item on any test, unless the instructions specifically say to do so.

(6) Keep testing materials (ie. spatial span board) out of view from the subject.

Telephone Questionnaire

Hello. My name is_____. I'm calling you concerning the study at the University of Ottawa on glucoregulation and memory. Do you remember having given your name as a potential participant? Are you still interested? Is this a good time for you to answer a few questions? O.K. Certain criteria have been established for this study. Based on these criteria, I will be asking you some questions to determine if you are eligible to participate in the study. Your answers are strictly confidential and they will be destroyed immediately if you do not participate in this study.

Reminders:

- If the subject responds Yes to any question, discontinue interview and go directly to statement 1
- If in doubt of an answer, prompt with more questions (see below)
- If you are unsure of an answer, tell subject that you will have to phone them back to continue the interview and phone Dr. Gagnon at the ROH (722-6521 ext. 7030)
- Yes = 1
  No = 0

(1) *Are you diabetic?*
If the subject is unsure, prompt with:
Are you taking any medication?
If the subject responds **yes - exclude**
If the subject responds **no - include**

(2) *Do you suffer from chronic hypoglycemia?*
Hypoglycemia = low blood sugar

(3) *Do you feel very weak if you do not eat?*
Very weak = **Do you feel that you're going to pass out if you do not eat?**

(4) *Do you suffer from important memory problems?*
Important = **Do you have difficulty remembering important dates or events? Or family meetings or gatherings etc..?**

(5) *Did you previously have a hemorrhage (intracranial)?*
CHANGE TO:
Did you previously have a hemorrhage or stroke?

(6) *Did you suffer from a brain tumor or lesion?*
CHANGE TO:
Did you previously suffer from a brain tumor or lesion or head injury?

(7) *Did you ever have any brain disease?*
Answers could include: Multiple sclerosis, Huntingtons, Parkinsons, Meningitis etc..

(8) *Do you have chronic hepatitis?*
Chronic = any type of hepatitis

(11) *How many alcoholic drinks did you take in the last week?*
(12) *How many alcoholic drinks did you take in the last month?*
(13) *How many alcoholic drinks does it take you to be intoxicated?*
ADD THESE QUESTIONS:
What do you drink?
Do you get intoxicated/drunk every time you drink?
Could you stop drinking (if you wanted to)?
If the subject has consumed **4 or more drinks/day for at least 1 month - exclude**
If the subject doesn't drink, do not continue asking the questions.
** *People generally under-report their drinking*

(14) *Do you take recreational drugs?*
Which ones?
How often did you take recreational drugs in the last week?
How often did you take recreational drugs in the last month?
This question applies to current drug use (ie. in the past month)
If the subject takes **cannabis** (ie. hash, hashish, pot, weed, grass, marijuana), **do not exclude unless they take it on a daily basis**
If the subject takes **any other recreational drug** (ie. acid, mushrooms, cocaine, crack) - **exclude**

★ **BEFORE ASKING** ***ARE YOU SEEING A PSYCHIATRIST PRESENTLY*****, ASK:**
Do you take any prescription drugs?
For example: Valium, Benzodiazepines, Zoloft, Prozac
If you are unsure, ask:
What do you take it for?
If you are still unsure, continue the interview and if they have not met any other exclusion criteria, tell them that you will have to check some information and that you will call them back. Phone Dr. Gagnon (722-6521 ext. 7030) to clarify the information and then call the subject back.

(17) *Are you currently being treated for depression?*
Any type of treatment (drugs, psychotherapy etc.) results in **exclusion** of subject

(18) *Do the following behaviours apply to you?*
**I cry easily*
I am irritable
**I have insomnia at the beginning or the middle of the night*
**I eat more or I eat less than usual*
These questions apply to current behaviours (ie. within the past month)
If the subject reports that the **all of the * items apply - exclude; otherwise, include**

QUESTIONS ON MEMORY (for older subjects only)

★ **If the subject answers "sometimes", ask them to please give a "yes" or "no" answer.**

Exclusion criteria:

- For questions (1) - (7), subject must have answered **Yes to more than 3 of the 7 questions and at least 2 of the 3 positive response must be to questions (2), (6) or (7).**

- For question (8), **do not exclude if the memory problems have been gradual.** However, **exclude if the memory problems came on suddenly.**

End of Telephone Questionnaire

Statement 1:
You appear to have met the criteria for our study and we would be glad if you could participate.

Statement 2:
We have set certain criteria for our study. Unfortunately, because you have (had) _____ and this is one of the criteria, we will not be able to include you in this study.

If they ask why, say:

We established certain criteria at the beginning of the study. One of the criteria is _____ . Because of this, we cannot include you in this study. However, if we conduct another study at a later date in which this is not a criteria, would you like us to call you then?

If they ask if they are too sick (or drink too much etc..), say:

No, that's not the case. We established certain criteria at the beginning of the study. One of the criteria is _____ . Because of this, we cannot include you in this study. However, if we conduct another study at a later date in which this is not a criteria, would you like us to call you then?

First Visit

Procedure:

(1) Ask subject to sign both consent forms (1 copy is for them to keep and 1 copy will go in their file)

(2) Explain to the subject that they should read the consent form over carefully and sign it.

(3) Answer any questions or concerns that the subject might have and then proceed with the questionnaires/tests.

(4) Weigh the subject and measure their height. Remember to measure both of these with their shoes off.

This morning I'll be asking you a few general questions which I would like you to answer as precisely as you can. Also, I'll be asking you to fill out a questionnaire (for older subjects - say, a couple of questionnaires). Do you have any questions?

Additional First Interview Information

ADD THIS QUESTION:

Are you currently taking any hormonal treatment?

Reminders:

How many years of schooling have you completed?
Schooling = from grade 1.

Do you smoke?
Include subject regardless of yes or no.

Do one or both of you parents suffer (has suffered) from diabetes?
Include subject regardless of yes or no.

Beck Depression Inventory (BDI)

This questionnaire consists of 21 groups of statements. After reading each group of statements carefully, circle the number (0, 1, 2, or 3) next to the one statement in each group which *best* describes the way you have been feeling the *past week, including today*. If several statements within a group seem to apply equally well, circle each one. *Be sure to read all the statements in each group before making your choice.*

Reminder:
If a subject circles more than one answer, score the highest one.

Mini Mental State Exam (MMSE)

(For older subjects only)

I'm going to ask you some questions now. Please answer them as precisely as you can.

I. ORIENTATION
(1) What is today's date?
(2) What is the year?
(3) What is the month?
(4) What day is today?
(5) Can you also tell me what season it is?
(6) What is the name of the place we are in?
(7) What floor are we on?
(8) What is the name of the city we are in?
(9) What is the name of the province we are in?
(10) What is the name of the country we are in?

II. REGISTRATION
I'm going to say 3 words to you and I want you to repeat them after me.
Say each word clearly and slowly for about one second each:
Ball, Flag, Tree.
Keep repeating the words (up to 5 trials) until the subject is able to say all three words.
Write down on score sheet how many trials the subject took to name them correctly. Score only the first trial.

III. ATTENTION AND CALCULATION

I would like for you to start with 100 and count backwards by 7s until I tell you to stop.

If they don't start counting right away, say:

You can do it now.

Repeat this instruction if the subject appear not to understand.

If they don't understand the instructions or cannot perform the task, say:

What is 100 minus 7 ... keep subtracting 7 until I tell you to stop

Stop the subject after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.

If they make an incorrect subtraction, but the following subtraction is correct, they only get one error (ie. 93, 86, *78*, 71, 64).

If the subject cannot perform this task (ie. if they make 4 or more incorrect subtractions or if they start adding instead of subtracting), **ask him/her to:**

Spell the word WORLD backwards

Score as the number of letters in the correct position.

Indicate on the sheet which task was scored.

IV. RECALL

Do you remember the 3 words I said to you earlier? Can you repeat them please?

If they cannot remember anything, say:

There were 3 objects....

If they still cannot remember anything, say:

There was one that was ball...

If they do remember the word (s) with one of the prompts, indicate this on the score sheet (ie. With prompt:____), but do not score the words as correct.

V. LANGUAGE

(1) Show the subject a watch and say:

What is this?

Show the subject a pencil and say:

What is this?

(2) **I'm going to say a sentence to you and I want you to repeat it to me:**

No ifs, ands, or buts.

If the subject answers incorrectly or asks for the sentence to be repeated, you may repeat it only once, but you must mark down on the score sheet that the phrase was repeated.

(3) **Take this paper in your right hand, fold it in half, and put it on the floor.**
Hand the subject a blank piece of paper after you say this.

(4) **I'm going to show you something and I want you to do what it says.**
Show the subject a piece of paper which says "CLOSE YOUR EYES".
If they don't open their eyes right away, say:

You can open you eyes now.

(5) Fold the sheet with CLOSE YOUR EYES in half so that the blank half of the page is showing. Say:

Write a sentence here.

(6) Fold the score sheet in half to expose the bottom half of 2nd side with the diagram. Say:

Could you please copy this design exactly as you see it on the page.
Take your time and draw it as carefully as you can.

If they make a mistake and are aware of it, allow them to reproduce it again on the sheet (only once)
If they make a mistake and are unaware of it, say:

Does this look exactly like this one? Then say:
Could you please draw it again here more carefully, to make it look exactly like this one?

Score the best reproduction, but indicate on the score sheet which reproduction (1st or 2nd) was scored.

Exclusion Criteria:
If a subject obtains a score of **23 or less, exclude** them from the study.

(For older subjects only)

Reminder:

(1) If you are unsure about any of the criteria below for a particular subject, call Dr. Gagnon and she will assess the subject

Diagnostic criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both

(1) memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)

(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

(c) agnosia (failure to recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (ie. planning, organization, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (eg. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

(2) systemic conditions that are known to cause dementia (eg. hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphillis, HIV infection)

(3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (eg. Major Depressive Disorder, Schizophrenia).

Code based on type of onset and predominant features:

With Early Onset: if onset is at age 65 years or below

290.11 With Delirium: if delirium is superimposed on the dementia

290.12 With Delusions: if delusions are the predominant feature

290.13 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.10 Uncomplicated: in none of the above predominates in the current clinical presentation

With Late Onset: if onset is after age 65 years

290.3 With Delirium: if delirium is superimposed on the dementia

290.20 With Delusions: if delusions are the predominant feature

290.21 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.10 Uncomplicated: in none of the above predominates in the current clinical presentation

Specify If:

With Behavioral Disturbance

Coding note: Also code 331.0 Alzheimer's disease on Axis II

End of 1st Visit

- Schedule 2nd appointment with subject. Let them know that you will be calling them the day before their next appointment to remind them of the appointment and that they have to fast.
- Bring subject to Health Center

Procedure:
Did you eat or drink anything at all since midnight? O.K. Before we start this morning, I'll measure your blood glucose level.

(1) Measure baseline blood glucose level. Record result.
(2) Give subject the sweet solution to drink after you have taken their measurement and you are waiting for the result and cleaning up.
(3) Record the time after they have finished drinking the sweet solution. The second glucose measurement will be taken 60 minutes after this time.
(4) Wait 5 minutes before beginning testing.

I'll be asking you to do a number of things this morning like solving a few number problems and remembering some lists of letters or words. Sometimes you will be asked to write down the answer and sometimes you will have to tell me the answer. You will find some of these tasks easy whereas others will be more difficult. Also, most people don't answer every question correctly or finish every item, but I would like you to give your best effort on all items. Do you have any questions?

Arithmetic

Materials:
Stopwatch & Blocks

Description:
For this subtest, the examinee is presented with a series of arithmetic word problems to be solved mentally, without the use of pencil or paper, and responds orally within a time limit.

General Instructions:
If the examinee obtains perfect scores (1 point) on both Items 5 and 6, give full credit for Items 1-4. Begin timing each item immediately after you read the problem to the examinee. A problem may be repeated once if the examinee requests, or if it is apparent the examinee failed to understand the task. However, timing always begins at the end of the first reading of the problem. The examinee may not use pencil and paper for any problem. However, do not discourage the examinee from using a finger to "write" on the table.

In the Completion Time column on the score sheet, record the exact amount of time the examinee takes to solve each problem, if it is within the time limit. The time limit for each item is provided in the Item Instructions and on the score sheet. Timing begins immediately after the problem has been read. Accurate recording of completion time is essential because the examinee may receive bonus points on Items 19 and 20.

In this first section, I will ask you to solve some arithmetic problems.

Remember:
Discontinue Rule:
Discontinue after 4 consecutive scores of 0

Reverse Rule:
If a score of 0 is obtained on Item 5 or 6, administer 1-4 in reverse sequence until two consecutive scores are obtained.

Scoring Rule:
Items 1-18; 0 or 1 pt. for each response
Items 19-20; 0, 1, or 2 pts

Form A

Discontinue Rule: 4 consecutive scores of 0 Item	Time Limit (In seconds)	Correct Response
1. Place three wooden disks, with approximately one-half inch between disks, in front of the examinee. Then say: How many disks are there all together?	15	3
2. Place seven disks, with approximately one-half inch between disks. Then say: How many disks are there all together?	15	7

	Discontinue after 4 consecutive scores of 0 Item	Time Limit (In seconds)	Correct Response
	3. Place seven wooden disks in front of the examinee and say: If you have 7 disks and take away 2 disks (remove 2 disks), how many do you have left?	15	5
	4. If you have 3 books and give 1 away, how many do you have left?	15	2
Start →	**5. How much is 4 dollars plus 5 dollars?**	15	$9.00
	6. If you buy 6 dollars' worth of gasoline and pay for it with a 10-dollar bill, how much change should you get back?	15	$4.00
	7. Soft drinks are sold 6 cans to a package. If you want 30 cans, how many packages must you buy?	30	5
	8. Chewing gum costs 25 cents per pack. How much would it cost to buy 6 packs?	30	$1.50
	9. How many hours will it take a person to walk 24 miles at the rate of 3 miles an hour?	30	8
	10. If you buy 7 20-cent mints and give the clerk 5 dollars, how much change should you get back?	30	$3.60
	11. If you have 18 dollars and spend 7 dollars and 50 cents, how much will you have left?	30	$10.50
	12. Jesse bought 6 pieces of chocolate for $1.60. An additional 20 cents sales tax was added to this price. How much did he pay for each chocolate including sales tax?	60	30 cents

Discontinue Rule: 4 consecutive scores of 0 Item	Time Limit (In seconds)	Correct Response
13. The price of shirts is 2 for 31 dollars. What is the price of 1 dozen shirts?	60	$186.00
14. What is the average of these numbers: 10, 5, and 15?	60	10
15. A family bought some second-hand furniture for two-thirds of what it cost new. They paid 400 dollars for it. How much did it cost new?	60	$600.00
16. A family drove 215 miles in 5 hours. What was their average speed in miles per hour?	60	43 mph
17. A coat that normally sells for 60 dollars is reduced by 15 percent during a sale. What is the price of the coat during the sale?	60	$51.00
18. Chris has two times as much money as Robert. Chris has ninety-nine dollars. How much money does Robert have?	60	$49.50
19. Linda had 8 yellow paper clips, 5 green paper clips, and 7 orange paper clips. She picked out one paper clip without looking. What was her chance of picking out a green paper clip?	60	1 of 4 or 5 of 20
20. If 8 machines are needed to finish a job in 6 days, how many machines would be needed to finish the job in one-half day?	120	96

Discontinue Rule:
4 consecutive
scores of 0

	Item	Time Limit (In seconds)	Correct Response
	1. Place three disks, with approximately one-half inch between disks, in front of the examinee. Then say: How many disks are there all together?	15	3
	2. Place seven disks, with approximately one-half inch between disks. Then say: How many disks are there all together?	15	7
	3. Place seven disks in front of the examinee and say: If you have 7 disks and I take away 2 disks (remove 2 disks), how many do you have left?	15	5
	4. If you have 3 books and give 1 away, how many do you have left?	15	2
Start →	**5. How much is 6 dollars plus 3 dollars?**	15	$9.00
	6. If you buy 7 dollars' worth of gasoline and pay for it with a 10-dollar bill, how much change should you get back?	15	$3.00
	7. Soft drinks are sold 6 cans to a package. If you want 24 cans, how many packages must you buy?	30	4
	8. Chewing gum costs 25 cents per pack. How much would it cost to buy 8 packs?	30	$2.00
	9. How many hours will it take a person to walk 21 miles at the rate of 3 miles an hour?	30	7

Discontinue Rule:
4 consecutive scores of 0

Item	Time Limit (In seconds)	Correct Response
10. If you buy 8 20-cent mints and give the clerk 5 dollars, how much change should you get back?	30	$3.40
11. If you have 18 dollars and spend 9 dollars and 50 cents, how much will you have left?	30	$8.50
12. Jesse bought 9 pieces of chocolate for $1.60. An additional 20 cents sales tax was added to this price. How much did he pay for each chocolate including sales tax?	60	20 cents
13. The price of shirts is 2 for 41 dollars. What is the price of 1 dozen shirts?	60	$246.00
14. What is the average of these numbers: 15, 5, and 10?	60	10
15. A family bought some second-hand furniture for one-third of what it cost new. They paid 400 dollars for it. How much did it cost new?	60	$1200.00
16. A family drove 315 miles in 5 hours. What was their average speed in miles per hour?	60	63 mph
17. A coat that normally sells for 80 dollars is reduced by 15 percent during a sale. What is the price of the coat during the sale?	60	$68.00
18. Chris has two times as much money as Robert. Chris has eighty-nine dollars. How much money does Robert have?	60	$44.50

Discontinue Rule:
4 consecutive
scores of 0

Item	Time Limit (In seconds)	Correct Response
19. Linda had 7 yellow paper clips, 8 green paper clips, and 5 orange paper clips. She picked out one paper clip without looking. What was her chance of picking out an orange paper clip?	60	1 of 4 or 5 of 20
20. If 9 machines are needed to finish a job in 6 days, how many machines would be needed to finish the job in one-half day?	120	108

Scoring:
For each item, record the response verbatim and the time the examinee takes to respond. Consider a response correct if the numerical quantity is correct, regardless of whether appropriate units (eg. dollars and cents) are included in the response. In addition, give credit if the examinee spontaneously corrects a wrong response within the time limit.

If the examinee obtained perfect scores on Items 5 and 6, give 1-point credit for each of Items 1-4. If some but not all reversal items were administered because the examinee responded correctly to two consecutive items, give 1-point credit for each of the unadministered reversal items. If the examinee responds correctly *after* the time limit, record 0 point for the response.

For items 1-18, record 1 point for each correct response provided within the time limit. For items 19 and 20, record 2 points for each correct response provided in 1-10 seconds or 1 point for a correct response provided in 10-120 seconds.

Maximum Score: 22 points

Digit Symbol – Coding

Materials:
Stopwatch
Two No. 2 graphite pencils without erasers

Description:
For Digit Symbol-- Coding, the examinee copies symbols that are paired with numbers. Using a key, the examinee draws each symbol under its corresponding number. The examinee's score is determined by the number of symbols correctly drawn within the 120-second time limit.

General Directions:
A smooth drawing surface must be provided. If the table has a rough surface, the Test Sheet should be placed on a clipboard, a piece of cardboard, or another flat surface.

If the examinee asks what they should do if they make a mistake, encourage them to continue to work as fast as they can. However, do not discourage examinees from making spontaneous corrections unless they do so repeatedly and it impedes their performance.

If, after completing a row, an examinee tries to complete the next row, remind the examinee to start at the beginning of the row and not to skip any.

Remember:
Discontinue Rule:
Discontinue after 120 seconds.

In this section, I'm going to ask you to copy some symbols.

Place the Digit Symbol – Coding Test in front of the examinee. Hand him or her a pencil without an eraser, point to the key above the test items, and say:

> **Look at these boxes. Notice that each has a number in the upper part and a special mark in the lower part. Each number has its own mark.**

Point to 1 and its mark in the key, then 2 and its mark. Then point to the seven squares located to the left of the heavy black line and say:

> **Now look down here where the squares have numbers in the top part, but the squares at the bottom are empty. In each empty square, put the mark that should go there. Like this.**

Point to the first Sample Item, then point back to the key to show its corresponding mark, and say:

> **Here is a 2; the 2 has this mark. So I put it in this empty square, like this.**

Write in the symbol. Point to the second Sample Item and say:

> **Here is a 1; the 1 has this mark (point to the second Sample Item, then to the mark below the 1 in the key), so I put it in this square.**

Write in the symbol.
Point to the third sample Item and say:

> **This number is a 3; the 3 has this mark (point to the third square and to the mark below the 3 in the key). So I put it in this square (write in the symbol).**

After marking the three Sample Items, say:

> **Now you fill in the squares up to this heavy line.**

If the examinee makes an error on any of the Sample Items, correct the error immediately and review the use of the key. Continue to provide help if needed. Do not proceed with the subtest until the examinee clearly understands the task.

When the examinee completes a Sample Item correctly, offer encouragement by saying **Yes** or **Right**.

When all of the Sample Items have been completed, say:

> **Now you know how to do them. When I tell you to start, you do the rest of them.**

Point to the first square to the right of the heavy line and say:

> **Begin here and fill in as many squares as you can, one after the other without skipping any. Keep working until I tell you to stop. Work as quickly as you can without making any mistakes.**

Sweep you finger across the first row with you finger and say:

> **When you finish this line, go on to this one.**

Point to the first square in the second row. Then point to the heavy black line and say:

> **Go ahead.**

Begin timing.

If the examinee omits an item or starts to do only one type (eg. only the 1s), say:

> **Do them in order. Don't skip any.**

Point to the first item omitted and say:

> **Do this next one.**

Provide no further assistance except to remind the examinee to continue until instructed to stop.
At the end of 120 seconds, say Stop.

Scoring:
Record 1 point for each correctly drawn symbol completed within the 120-second time limit. *Responses to the seven Sample Items are not included in the examinee's score.* Do not give credit for items completed out of sequence.

Use the Digit Symbol Scoring Template to check the examinee's responses and record the score on the score sheet.

A response is scored as correct if it is clearly identifiable as the keyed symbol, even if it is drawn imperfectly or if it is a spontaneous correction of an incorrect symbol.

Maximum Score: 133 points

Description of Modified Brown Peterson Task:

MBP20x: MBP stands for modified Brown-Peterson. The appendix "x" indicates that there are several versions of the same program; these versions are called: a, b, c, and d. Thus, there are 4 versions of this program (MBP20A, MBP20B, etc.). The different versions implement a counterbalancing scheme in the presentation of the lists of stimuli.

In the MBP task, subjects are given ORALLY series of 3 consonants at a fairly rapid rate (1 items per second). The screen must be turned away from the subject. The experiment reads the consonant from the screen and speaks them out as they appear. At the end of each series, subjects write the consonants they heard on a lined sheet of paper.

Each version of MBP20x involves 3 blocks. In Block 1, a tone occurs immediately after the last consonant to prompt the subject to recall as much as he/she can remember. These trials provide a baseline. In Blocks 2 and 3, the tone occurs after a delay of 20 sec. This delay may be "filled" or empty. When it is filled, the subject must count backward in 3s from a number given by the experimenter until a tone is heard. This interpolated task typically hinders recall. When the interval is empty, the subject simply waits for the tone to occur. In both cases, the subjects can start writing down the consonants after the tone. In MBP20A and MBP20C, Block 2 involves counting backward and Block 3 involves waiting. In MBP20B and MBP20D involves the reversed sequence. Within each block the series of 3 consonants are presented in random order and this order differs for each subject.

Each block begins with 4 practice trials and continues with 10 experimental trials.

Procedure:

(1) Check the list to see what version of MBP should be administered. The list will tell you what version to administer depending on the subject number and the visit number.

(2) Sit directly in front of the computer screen and have the subject sit to the side because they will not be allowed to see the computer screen when the test begins.

(3) If you are in room 107, press ALT F5 to bypass Windows and go into Dos mode. Type CD MEL2

(4) At C:\MEL2>, Type run mbp20_. Press Enter.

(5) Type subject number (0 for a practice trial) and press enter.

(6) Type session number (1 or 2 (ie. 2nd or 3rd visit)) and press enter. Type Y when asked if you want your data logged.

(7) Instructions for MBP appear. Read them to subject while they are looking at the screen as well. Do not say "we will start with a bit of practice...". Press space bar.

(8) Instructions for Block 1 (baseline) appear. Read them to the subject while they are looking at the screen. Say:
There will be 14 trials. The first 4 will be practice trials.
Press space bar.

(9) **PUT UP DIVIDER TO BLOCK THE SCREEN FROM THE SUBJECT.**

Block 1

(10) Hand the subject an MBP Block 1 recall sheet.

(11) Screen says "Ready?". Ask subject if they are ready. Press space bar to say the letters.

(12) Say letters as they are presented on the screen.

(13) Screen says "Time to recall". Press the space bar when they are finished.

(14) This procedure (10-12) repeats itself for 3 more practice trials and 10 experimental trials.

Block 2

(15) Instructions for Block 2 appear. Read them to the subject and press space bar.

(16) More explicit instructions for Block 2 appear. Block 2 will consist of either counting or waiting trials. Read the instructions to the subject. Say:
There will be 14 trials. The first 4 will be practice trials.
Press space bar.

(17) Hand the subject an MBP Block 2 recall sheet.

(18) Screen says "Ready?". Ask them if they are ready. Press space bar to say the letters (and the number if this are the counting trials)

(19) Say letters as they are presented on the screen. If this is a counting trial, say the number as well.

(20) The subject will have to either wait silently for 20 seconds or count backward by threes from the number you said, for 20 seconds.

Do not let the subject rehearse the letters.

If it is a counting trial and they are not counting backwards, say:
Please count backward by threes from the number I said.

(21) After 20 seconds, the screen says "Time to recall". Press the space bar when they are finished.

(22) This procedure (17-20) repeats itself for 3 more practice trials and 10 experimental trials.

Block 3

(23) Instructions for Block 3 appear. Read them to the subject and press space bar.

(24) More explicit instructions for Block 3 appear. Block 3 will consist of either counting or waiting trials. Read the instructions to the subject. Say:
There will be 14 trials. The first 4 will be practice trials.
Press space bar.

(25) Hand the subject an MBP Block 3 recall sheet.

(26) Screen says "Ready?". Ask them if they are ready. Press space bar to say the letters (and the number if this are the counting trials)

(27) Say letters as they are presented on the screen. If this is a counting trial, say the number as well.

(28) The subject will have to either wait silently for 20 seconds or count backward by threes from the number you said, for 20 seconds.

Do not let the subject rehearse the letters.

If it is a counting trial and they are not counting backwards, say:
Please count backward by threes from the number I said.

(29) After 20 seconds, the screen says "Time to recall". Press the space bar when they are finished.

(30) This procedure (25-28) repeats itself for 3 more practice trials and 10 experimental trials.

(31) After the Block 3 has been completed, the screen says "Test completed - thank you for your patience"

(32) Screen goes directly to C:\MEL2>. The computer is now ready for the next computer task.

Symbol Search

Materials:
Stopwatch
Two No. 2 graphite pencils without erasers

Description:
For this subtest, the examinee visually scans two groups of symbols: a target group (composed of two symbols) and a search group (composed of five symbols) and indicates whether either of the target symbols matches any of the symbols in the search group. The examinee responds to as many items (ie. rows) as possible within a 20-second time limit.

General Directions:
Use the Sample Items to explain and demonstrate the task to the examinee. If the examinee does not understand the instructions or appears confused, repeat the explanation and demonstration of the task using the Sample Items. Then allow the examinee to do the Practice Items. If the examinee responds incorrectly on the Practice Items, give the help needed for him or her to understand the task, as indicated in the instructions for the test items. Do not proceed with the subtest unless the examinee clearly understands the task. When necessary, remind the examinee to respond to the test items in order.

The Sample Items and Practice Items are not timed. Start timing only after finishing the directions for the test items.

Remember:
Discontinue Rule:
Discontinue after 120 seconds.

In the next task, I want you to look at two target shapes. Then I want to see if you can find either one of them in the group of shapes next to them.

Turn to the Symbol Search test sheets and place them in front of the examinee. To demonstrate the task, point to Sample 1 and say:

Sample Item 1:

Look over here (point to all the shapes in a sweeping motion). **Notice there are two shapes on the left side** (point to the target group) **and a group of shapes on the right side** (point to the search group).

You are to mark the "YES" box if one of shapes on the left side is the same as any of the shapes from the group on the right side (point to the search group).

For example, this shape here (point to the first symbol in the target group) **is the same as this shape here** (point to the matching symbol), **so I will mark the "YES" box like this** (draw a slash in the "YES" box).

Sample Item 2:

For this second item, this shape here (point to the second symbol in the target group) **is the same as this shape here** (point to the matching symbol), **so I will mark the "YES" box like this** (draw a slash in the "YES" box).

Sample Item 3:

Mark the "NO" box if none of the shapes on the left side (point to the target group) **are the same as any of the shapes from the group on the right side** (point to the search group). **In this case, none of the shapes here** (point to the target group) **is in the group over here** (point to the search group), **so I will mark the "NO" box like this** (draw a slash in the "NO" box).

Practice Items:

Hand the subject a pencil without an erase, point to the three Practice Items and say:

Now you do these. Go ahead.

Answers to Practice Items 1-3 are Yes, Yes, and No, respectively. If the examinee responds correctly to a Practice Item, offer encouragement such as **Good** or **Right.** Then say:

Now you know how to do them.

After the examinee completes all three Practice Items, proceed with the subtest.

If the examinee responds incorrectly to a Practice Item, provide any help needed, similar to the demonstration and explanation given in the Sample Items. For example, if the examinee marks "NO" when a target symbol appears in the search group, say:

> **That's not quite right. Look here (point to the target symbol in the group on the left). Now look over here (point to the matching symbol in the search group). Here is the same shape. The shapes are the same, so you should mark the "YES" box.**

If the examinee incorrectly marks "YES" when a target symbol does not appear in the search group, say:

> **That's not quite right. Look here (point to the target symbols). Here are two shapes, but when we look over there (point to the search group), none of the shapes is the same. The shapes are not the same, so you would mark the "NO" box.**

Do not proceed until the examinee clearly understands the task. When the examinee successfully completes the Practice Items, proceed with the subtest.

Items 1-60:

Open the response booklet to expose the first two pages of the subtest and say:

> **When I tell you to start, you do these the same way. Begin here (point to the top row on the page to the examinee's left) and do as many as you can. When you finish the first page, go on to the next page and so on (briefly show the third and fourth pages of the test items and fold the booklet so that only the first page of items shows).**
>
> **Most people don't do all of them. Work as quickly as you can without changing your answers. Don't skip any items and don't stop until I tell you to do so. Any questions?**

Explain further if necessary. Then say:

> **Okay. Ready? Begin.**

Begin timing.
If necessary, remind the examinee to respond to the test items in order. Give no further assistance. At the end of 120 seconds, say: **Stop.**

Scoring:
Place the Symbol Search Scoring Template over the response columns of each page of the Symbol Search response booklet, making sure that the template is correctly aligned. Above each column is a small number that corresponds to the page number of the Symbol Search response booklet.

A response is incorrect if both "YES" and "NO" are marked unless it is clear that one response is the intended response; score the clearly intended response. For example, an examinee may mark the "NO" box, clearly cross out that mark, and then mark the "YES" box. In such case, consider the response to be "YES".

Record the number of correct and incorrect responses at the bottom of each page of the booklet. Separately sum the subtotals of the correct responses and the subtotals of the incorrect responses and transfer these totals to the score sheet. Subtract the total number of incorrect responses from the total number of correct responses. *The score of the test is the number of correct responses minus the number of incorrect responses. Items that the examinee did not attempt (either skipped or did not reach before time elapsed) are not included in these score calculations.*

Maximum Score: 60 points

Digit Span

Description:
Digit Span is composed of two tasks administered independently of each other: Digits Forward and Digits Backward. On both tasks, the examiner reads a series of number sequences to the examinee. For each Digits Forward item, the examinee is required to repeat the number sequence in the same order as presented. For Digits Backward, the examinee is required to repeat the number sequence in the reverse order.

General Directions:
The two parts of Digit Span - Digits Forward and Digits Backward - are administered separately. *Administer Digits backward even if the examinee obtains a score of 0 on Digits Forward. Administer both trials of each item even if the examinee passes Trial 1.* Read the digits at the rate of one per second, *dropping your voice inflection* slightly on the last digit in the sequence. Pause to allow the examinee to respond.

Digits Forward

I am going to say some numbers. Listen carefully, and when I am through, I want you to say them right after me. Just say what I say.

Remember:
Discontinue Rule:
If a score of 0 is obtained on both trials of any item
For both Digits Forward & Backward, administer both trials of each item even if Trial 1 is passed.
Administer Digits Backward even if examinee scores 0 on Digits Forward.

Scoring Rule:
Each Trial: 0 or 1 pt. for each response
Item score = Trial 1 + Trial 2

Take score sheet and begin on Trial 1 of Item 1 for Digits Forward.

Digits Backward

After subject has completed Digits Forward (or scored 0 on both trials of any item), say:

Now I am going to say some more numbers. But this time when I stop, I want you to say them backward. For example, if I say 7-1-9, what would you say?

If the examinee responds correctly (9 - 1 - 7), say:

> **That's right.**

Proceed to Trial 1 of Item 1. However, if the examinee responds incorrectly, provide the correct response and say:

> **No, you would say 9 - 1 - 7. I said 7 - 1 - 9, so to say it backward, you would say 9 - 1- 7. Now try these numbers. Remember, you are to say them backward: 3 - 4 - 8.**

Do not provide any assistance on this example or any of the items.
Whether or not the examinee responds correctly (ie. 8 - 4 - 3), proceed to Trial 1 of Item 1.

Take score sheet and begin on Trial 1 of Item 1 on Digits Backward.

Scoring:
Each item is scored 0, 1, or 2 points as follows:

- 2 points if the examinee passes both trials
- 1 point if the examinee passes only one trial
- 0 points if the examinee fails both trials

Maximum Score on Digits Forward: 16 points
Maximum Score on Digits Backward: 14 points
Maximum Score on Digit Span: 30 points

Materials:
Spatial Span Board

Remember:
Discontinue Rule:
Discontinue of scores of 0 are obtained on both trials of an item.

Spatial Span – Forward

Place the Spatial Span Board on the table with the cube numbers facing you and with the board centered at the examinee's midline, so that he or she can easily reach the cubes. Say:

Now I want you to do exactly what I do. Touch the blocks I touch, in the same order.

Use the score sheet for the tapping sequence. Tap out the sequence for Trial 1 of Spatial Span Forward Item 1 at a rate of one cube per second.

Continue administering the items for Spatial Span Forward, using the sequences on the score sheet. Record the examinee's responses. If the criterion for discontinuing is met, or if all Spatial Span Forward items have been administered, proceed with Spatial Span Backward.

Spatial Span – Backward

Now I am going to touch some more blocks. This time when I stop, I want you to touch the blocks backward, in the reverse order of mine. For example, if I touch this block (Cube 3), **then this one** (Cube 5), **what would you do?**

If the examinee responds correctly, say:

> **That's right. Here's the next one. Remember to touch them in the reverse order.**

Then proceed with Item 1.

If the examinee responds incorrectly on the 3 - 5 example sequence, point appropriately as you say :

> **No, I touched this one, then this one; so, to do it in reverse, you would touch this one, then this one. Now let's try another one. If I touch this one** (Cube 9), **then this one** (Cube 1), **what would you do?**

Whether the examinee succeeds or fails on the second example, proceed to Item 1.

Continue administering the items for Spatial Span Backward (using the sequences on the score sheet) until the criterion for discontinuing is met or until all items are administered. Record the examinee's responses.

Maximum Score on Spatial Span Forward: 16 points
Maximum Score on Spatial Span Backward: 16 points
Maximum Score on Spatial Span: 32 points

Materials:
Tape Recorder
Cassette tape with pre-recorded story (recorded twice for ease of administration)
Blank cassette tape

I am going to play a short story for you. Listen carefully and try to remember it just the way it is said, as close to the same words as you can remember. When it is finished, I want you tell me everything that was said. You should tell me all you can remember even if you're not sure. Are you ready?

Play the cassette tape with the pre-recorded story (Story A or B) on the tape recorder. After playing the story, remove cassette tape with pre-recorded story and insert blank cassette tape. Then say:

> **Tell me everything you can remember about this story. Start at the beginning.**

Begin recording. After the examinee has recalled as much of the story as he or she can, and you have recorded the examinee's response, say:

> **I am going to play the same story for you again. Listen carefully and try to remember it just the way it is said, as close to the same words as you can. When it is finished, tell me everything you can remember. Are you ready?**

Insert the cassette tape with the pre-recorded story and play the story. After playing the story, remove cassette tape with pre-recorded story and insert blank cassette tape. Then say:

> **Tell me everything you can remember about this story. Start at the beginning.**

Begin recording. After the examinee has recalled as much of the story as he or she can, and you have recorded the examinee's response, say:

> **I want you to remember as much of this story as you can because I will ask you to tell me the story again later.**

Scoring:
0-1 point for each story or thematic unit.
See scoring manual for scoring criteria.

Rey (or Taylor) Complex Figure Task

Purpose:
The purpose of this test is to assess visuospatial constructional ability and visual memory.

Materials:
Stimulus card
#2 black lead pencil with an eraser
Stopwatch

Administration:
The Rey (or Taylor) Complex Figure Task (RCFT or TCFT) consists of three separate tasks. First, the respondent views the complex figure stimulus card and copies the figure onto a blank sheet of paper.

After the respondent indicates that he or she has completed the Copy drawing, the stimulus figure and the drawing are immediately removed from view.

Three minutes of unrelated verbal activity follow. The Immediate Recall trial is administered next. This involves the respondent drawing the figure from memory on a blank sheet of paper.

Then, 30 minutes after the respondent completed the Copy trial, he or she completes the Delayed Recall trial by again drawing the figure memory.

It should be emphasized that the normative data for the RCFT were collected using a 3-minute delay interval between Copy and Immediate Recall, and a 30-minute delay interval between Copy and Delayed Recall. Deviation from this procedure may affect the validity and utility of the obtained results.

Reminders:
It is imperative that the respondent never glimpses any RCFT materials that contain the stimulus figure, parts of the stimulus figure, or his or her own previous drawings. Respondents may be encouraged and praised for their efforts, but not for their drawings. The respondent is permitted to erase, but he or she should never trace the figure or be given a straight edge or ruler to use in drawing.

Label each sheet according to trial (ie. Copy, Immediate Recall, and Delayed Recall).

Copy

Put a plain sheet of 8.5 x 11 paper on the table so that the long edge of the paper is along the edge of the table in front of the subject. Center the sheet in front of the respondent. Place the stimulus card directly above the plain sheet and hand the respondent a #2 pencil. Then say:

I would like you to copy that figure onto this sheet of paper. Please copy it as carefully as you can.

After the subject indicates that he or she understands the nature of the task, begin timing the drawing as the respondent starts copying the figure. The instructions may be repeated or paraphrased as often as necessary to ensure that the respondent understands the task. The respondent's effort may be encouraged, should he or she have difficulty with the task. However, no additional hints or cues about the figure may be given. The respondent is permitted to erase, but he or she may never trace the figure or be given a straight edge or ruler to use in drawing.

As the respondent is drawing the figure, draw along with them on your sheet containing the figure, noting the sequence and organization of their reproduction. Use numbers to indicate the exact sequence employed by the respondent.

The respondent may rearrange the Copy trial response sheet and the stimulus card according to personal preference. However, the respondent should not rotate either the response sheet or stimulus card more than 25 degrees from the portrait orientation. If this occurs, correct the respondent by placing the response sheet, stimulus card, or both back in the proper orientation. If the respondent rotates either the response sheet or stimulus card a second time, do not correct him or her, but do note this rotation in the test booklet for later reference.

When the respondent is finished copying the figure, immediately remove both the stimulus card and the response sheet from view. Note the length of time (in seconds) required to copy the figure and record this on their response sheet.

Record the time of day that the Copy trial was completed on your index card.

As the Immediate and Delayed Recall trials are measures of incidental visuospatial memory, the respondent should NOT be told this is a memory test or that he or she will be asked later to draw the figure from memory.

The Immediate Recall trial is administered 3 minutes after the Copy trial is completed. It is important that the subject is engaged and actively performing a verbal task during the delay interval.

Put a plain sheet of 8.5 x 11 paper on the table so that the long edge of the paper is along the edge of the table in front of the subject. Center the sheet in front of the respondent. Hand the respondent a #2 pencil. Then say:

A short time ago I had you copy a figure. I would like you to draw that figure again, but this time from memory.

There is no time limit on the immediate recall task however, record the length of time the respondent requires to produce the Immediate Recall drawing. The respondent's effort may be encouraged should she or he have difficulty with the task. However, no additional cues or hints about the stimulus figure may be given.

As in the Copy trial, the order of approach should be recorded. Draw along with the respondent as they are drawing the figure. Draw on a blank sheet of paper, noting the sequence and organization of their reproduction. Use numbers to indicate the exact sequence employed by the respondent.

After the subject has recalled as much of the drawing as they can, immediately remove the response sheet from view. Note the length of times (in seconds) required to draw the figure on the response sheet.

The respondent should NOT be told that he or she will be asked later to draw the figure from memory.

Scoring:
See scoring and profiling procedures for explicit criteria on how to score the figures. Fill in the score sheet for the figure for each subject.

Maximum Score: 36 points

Verbal Free Recall

Description of MEL:
MEL stands for Micro Experimental Laboratory. It is a software package for designing psychological experiments. It has many outstanding features (despite the fact that it runs under DOS rather than Windows). One of them is high timing accuracy.

Description of Verbal Free Recall Programs:
VFR12 is a program that controls a verbal free recall task. It presents a practice list of 12 items and 4 experimental lists of 12 items. Each list is followed by a recall interval of 2 min. The presentation rate is 2 sec per item.

VFR20 is a program that also controls a verbal free recall task. It presents a practice list of 12 items and 4 experimental lists of 20 items. Each list is followed by a recall interval of 2 min. The presentation rate is 2 sec per item.

VFR20A is a program identical to VFR20 with one difference: The presentation rate is 4 sec per item. This modification was made in case we obtain a very poor recall performance with older subjects.

We will be using VFR20 for this study.

Procedure:

(1) Have the subject sit directly in front of the screen and sit next to them.

(2) Choose Option 1 (Micro Experimental Laboratory). Press Enter and C:\MEL2> appears.

(3) Type run vfr 20

(4) Press Enter.

(5) Type subject number (0 for a practice trial) and press enter.

(6) Type session number (1 or 2 (ie. 2nd or 3rd visit)) and press enter.

(7) Type Y when asked if you want your data logged.

(8) Instructions for VFR appear. Read them to subject while they are looking at the screen as well. Press space bar.

(9) Warning of Practice List appears.

(10) Press space bar and computer beeps. Words start flashing (1 every 2 seconds) until 12 have been flashed. Computer beeps and the it is time to recall. The screen says "time to recall". Hand the subject a VFR practice recall sheet. They have 1 minute to recall as much as they can. However, you may allow them additional time up to 2 minutes to recall as much as they can.

(11) After the 1-minute recall, the computer beeps. Press the space bar and the Warning List for the 1st Experimental List appears.

(12) Press space bar and computer beeps. Words start flashing (1 every 2 seconds) until 20 have flashed. Computer beeps and it is time to recall. The screen says "time to recall". Hand the subject a VFR (1st List) recall sheet. They have 1 minute to recall as much as they can. However you may allow them additional time up to 2 minutes to recall as much as they can.

(13) This procedure repeats itself for the 2nd, 3rd and 4th Experimental Lists with the corresponding VFR recall sheets.

(14) After the 4th Experimental List has been recalled, the screen says "Test completed - thank you for your patience"

(15) Screen goes directly to C:\MEL2>. The computer is now ready for the next computer task.

Logical Memory II - Delayed Recall and Recognition

★ **Administer LM II 25-35 minutes after LM I.**

Materials:
Tape Recorder
Blank cassette tape

Recall

Do you remember the story I played for you a little while ago? I want you to tell me the story again. Tell me everything that you can remember about the story and start at the beginning.

Insert blank cassette tape (same tape as in Logical Memory I) and record.

For Story A: If the examinee does not recall any story units, say:

The story was about a woman who was robbed.

For Story B: If the examinee does not recall any story units, say:

The story was about a weather bulletin.

Do not give any further help other than general encouragement. Note on the score sheet whether the reminder was given.

When the examinee has recalled as much of Story A as he or she can, and you have recorded the examinee's response, proceed to Recognition.

Recognition

I am going to ask you some questions about the story. If you are not sure of the answers, give your best guess.

Read the Recognition questions for Story A or Story B from the score sheet and record the examinee's responses.

Scoring:
0 - 1 point for each story or thematic unit.
See scoring manual for scoring criteria.

For this subtest, the examinee is read a combination of numbers and letters and is asked to recall the numbers first in ascending order and then the letter in alphabetical order. Each item consists of three trials, and each trial is a different combination of numbers and letters.

General Directions:
Administer all practice trials. For each Practice Item and item trial, say each combination at a rate of one number or letter per second. Allow the examinee ample time to respond (correct responses are in parentheses).

Remember:
Discontinue Rule:
After failure on all 3 trials of an item

Scoring Rule:
0 or 1 pt. for each response
Item score = Trial 1 + Trial 2 + Trial 3

I am going to say a group of numbers and letters. After I say them, I want you to tell me the numbers first, in order, starting with the lowest number. Then tell me the letters in alphabetical order. For example, if I say B - 7, your answer should be 7 - B. The number goes first then the letter. If I say 9 - C - 3, then your answer should be 3 - 9 - C, the numbers in order first, then the letters in alphabetical order. Let's practice.

6 - F	(6 - F)	If the examinee makes an error in any Practice Item, correct him or her and repeat the instructions as necessary. Say, **No, in this case the correct answer would be _____. Remember, the numbers go first, in order, starting with the lowest number and then the letters in alphabetical order.** Even if the examinee fails all Practice Items, continue with the subtest.
G - 4	(4 - G)	
3 - W - 5	(3 - 5 - W)	
T - 7 - L	(7 - L - T)	
1 - J - A	(1 - A - J)	

Take score sheet and begin on Trial 1 of Item 1. Say:

Now we'll continue.

Scoring:
Record the examinee's response to each trial *verbatim*, the trial score, the item score, and the total subtest raw score.

For each trial of an item, score 1 point for each correct response, 0 points for each incorrect response. A response is incorrect if a number or letter is omitted or if the numbers or letters are not said in the specified sequence. *As long as the numbers and letters are recalled in sequence, give credit if the examinee gives the letters in sequence before the numbers.* Sum the trial scores to obtain the item scores; sum the item scores to obtain the total score.

Each item is scored 3, 2, 1, or 0 points as follows:

- 3 points if the examinee passes all three trials
- 2 points if the examinee passes two trials
- 1 point if the examinee passes only one trial
- 0 points if the examinee fails all three trials

Maximum Score: 21 points

Rey (or Taylor) Complex Figure Task - Delayed Recall

★ **The Delayed Recall trial is administered 30 minutes after the Copy trial is completed.**

Administer verbal tasks to the respondent during the interval between completion of the Immediate Recall trial and Delayed Recall trial. It is important that the respondent is engaged and actively performing a verbal task during the delay interval.

Put a plain sheet of 8.5 x 11 paper on the table so that the long edge of the paper is along the edge of the table in front of the subject. Center the sheet in front of the respondent. Hand the respondent a #2 pencil. Then say:

A short time ago, I had you copy a figure. I would like you to draw that figure again, but this time from memory.

Record the time of day that the Delayed Recall trial commenced on your index card. There is no time limit on the immediate recall task however, record the length of time the respondent requires to produce the Delayed Recall drawing. The respondent's effort may be encouraged should she or he have difficulty with the task. However, no additional cues or hints about the stimulus figure may be given.

As in the Copy trial, the order of approach should be recorded. Draw along with the respondent as they are drawing the figure. Draw on a blank sheet of paper, noting the sequence and organization of their reproduction. Use numbers to indicate the exact sequence employed by the respondent.

After the subject has recalled as much of the drawing as they can, immediately remove the response sheet from view. Note the length of times (in seconds) required to draw the figure on the response sheet.

Scoring:
The scoring for this drawing is identical to that of Copy and Immediate Recall.

Order Recall

Description of Order Recall:
Order Recall or OR20 is a program very similar to VFR20. It presents 2 lists of 20 items. The presentation rate is 2 sec per item. The main difference between OR and VFR is that with OR all 20 items of each list is provided to the subject in alphabetical order. The subject does not have to recall the items. He/she simply must rewrite them in the same order as they were presented.

Procedure:

(1) Have subject sit directly in front of the computer and sit next to them.

(2) At C:\MEL2>, Type run or20. Press Enter.

(3) Type subject number (0 for a practice trial) and press enter.

(4) Type session number (1 or 2 (ie. 2nd or 3rd visit)) and press enter. Type Y when asked if you want your data logged.

(5) Instructions for OR appear. Read them to subject while they are looking at the screen as well. Press space bar.

(6) Warning of Practice List appears.

(7) Press space bar and computer beeps. Words start flashing (1 every 2 seconds) until 12 have been flashed. Computer beeps and the it is time to recall. The screen says "time to recall". Hand the subject an OR practice recall sheet. They have 1 minute to recall the order of the words. However you may allow them additional time up to 2 minutes to recall as much as they can.

(8) After the 1-minute recall, the computer beeps. Press the space bar and the Warning List for the 1st Experimental List appears.

(9) Press space bar and computer beeps. Words start flashing (1 every 2 seconds) until 20 have flashed. Computer beeps and it is time to recall. The screen says "time to recall". Hand the subject an OR recall sheet (1st list). They have 1 minute to recall the order of the words. However you may allow them additional time up to 2 minutes to recall as much as they can.

(10) This procedure repeats itself for a 2nd Experimental List with the corresponding OR recall sheet.

(11) After the 2nd Experimental List has been recalled, the screen says "Test completed - thank you for your patience"

(12) Screen goes directly to C:\MEL2>. The computer is now ready for the next computer task.

End of Second Visit

- After the testing has been completed, return to the Additional First Interview Information page and ask the Additional Second Interview Information question: "What was the solution you drank today - real sugar or artificial?"

- Schedule appointment for third visit. Let them know that you will be calling them the day before their next appointment to remind them of the appointment and that they have to fast.

End of Third Visit

- Pay subject $20.00

- Ensure that you obtain a receipt for the payment.