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The Effects of Glucose Regulation on the Neuropsychological Performance of Young Nondiabetic Adults

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The Effects of Glucose Regulation on the Neuropsychological Performance of Young Nondiabetic Adults

Doctoral Dissertation

By

Nesrine Awad

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Pages 2-6 missing.

Foreward

Sections of the literature review in the Introduction have been published elsewhere (Please see Journal of Clinical and Experimental Neuropsychology, 26 (8), 1044 – 1080, "The relationship between Impaired Glucose Tolerance, Type 2 diabetes, and cognitive function" by Awad, N., Gagnon, M., & Messier, C. (2004), and Neurological Research, 26 (5), 567-572, "The relationships between atherosclerosis, heart disease, type 2 diabetes and dementia", by Messier, C, Awad, N., & Gagnon, M. (2004) for details). In addition, data on a subset of the study sample have also been analyzed and published, and can be found in Behavioural Neuroscience, 116 (4), 691-702, "Impact of peripheral glucoregulation on memory", by Awad, N., Gagnon, M., Desrochers, A., Tsiakas, M., & Messier, C. (2002).

Abstract

Glucose regulation, in both patients with diabetes and nondiabetes patients, has been shown to be associated with neuropsychological function, particularly episodic memory. The main purpose of this study was to examine this association in a large sample of young nondiabetic adults, using a repeated-measures design in which participants were assessed under both, glucose and saccharin conditions. Regression analyses revealed that glucoregulatory indices based on evoked glucose levels significantly predicted the verbal memory performance of 135 young adults, independent of demographic and vascular risk factors. Repeated multiple analyses of variances using cognitive measures by function as dependent variables revealed that worse glucose regulators showed poorer verbal memory performance compared to better glucose regulators, with the performance of average glucose regulators falling in between. There was no effect of solution nor did gender interact with glucose regulation. Although worse regulators showed evidence of hyperinsulinemia, glucoregulatory indices calculated on the basis of insulin levels or fasting glucose levels were less sensitive to cognitive variability relative to indices based on evoked glucose levels. Cardiovascular risk factors were indeed associated with hyperinsulinemia, however, these did not predict cognitive performance in this young group. These results were discussed in light of medial temporal lobe functions, including encoding and retrieval of information, and appear to be mediated by changes in lipid metabolism, insulin receptor distribution and function, and/or genetic susceptibility.

Introduction

Neuropsychological function associated with glucose regulation has been investigated using various methods, across several lines of research. These research areas will be reviewed in the following introduction. Specifically, early studies evaluating the cognitive functions of children and adults with life-long type 1 diabetes will initially be presented, including a review of the factors that are likely interacting with the cognitive functions of these individuals, such as hypoglycemic episodes and early age of onset of the disease. Studies investigating the neuropsychological performance of adults with the later onset type 2 diabetes will then be reviewed. This research area has recently proliferated with several reviews conducted to date. Two tables summarizing the data will be reviewed and include both cross-sectional and population studies. Factors that have reportedly contributed to some of the cognitive variation associated with type 2 diabetes include level of glucoregulatory control/severity of disease and vascular dysfunction will also be explored. In addition, the link between dementia and type 2 diabetes will also be briefly addressed in the review of longitudinal studies in this area. In another line of research, other investigations have demonstrated that varying levels of normal glucose regulation in both young and older adults also appear to be associated with cognitive functions. Given the purpose of the current study, these studies will be more thoroughly explored. The interaction between glucose ingestion and glucoregulatory status in nondiabetes patients, as well as possible peripheral and central mechanisms underlying such glucose-mediated effects on cognition will also be addressed. Finally, in light of some the limitations of previous studies, the objectives and

hypotheses for the present study will be outlined. I now turn to a brief introduction and rationale for the present study.

Glucose is the primary energy substrate of the brain. The human brain, which constitutes only 2% of the body weight, utilizes approximately 25% of total body glucose (Magistretti, 1999). The breakdown of glucose also provides necessary compounds for normal structure and function of neurons including neurotransmitters such as acetylcholine, and glutamate and GABA (Schulingkamp, Pagano, Hung, & Raffa, 2000). Brain glucose utilization is regionally heterogenous (Sokoloff et al., 1977) and is dependent on the functional activation of specific neuronal systems (Ginsberg, Prado, Dietrich, Busto, & Watson, 1987; Melzer et al., 1985; Roland, 1985).

Recently, it has been shown that hippocampal neuronal activation produced by training on a memory task, resulted in a decrease of extracellular glucose levels in the hippocampus (E. C. McNay, Fries, & Gold, 2000). This decrease was shown to be alleviated by peripheral glucose administration that also led to improvement in memory performance. Another study showed that the decrease of extracellular glucose levels in the hippocampus of aged rats was much more pronounced than in younger rats but could also be reversed by peripheral glucose injection (E C McNay & Gold, 2001). Furthermore, although peripheral glucose injections had an effect on extracellular glucose levels in the hippocampus, they did not increase extracellular brain glucose levels in the striatum, suggesting that the effects of these injections are restricted to regions that show increased metabolic activity during training in a memory task (E C McNay, McCarty, & Gold, 2001).

Early animal studies have demonstrated that glucose ingestion appears to differentially affect the performance of mice with varying levels of glucose regulation (Messier & Destrade, 1988; Messier, Pierre, Desrochers, & Gravel, 1998). Specifically, two strains of mice were investigated in these studies (Balb/cJ and Balb/cByJ), with the Balb/cJ strain showing lower glucose levels and high resistance to scoplolamine's amnestic effects compared to the Balb/cByJ. The studies revealed that only the Balb/cByJ showed improvements on an operant conditioning task following glucose ingestion. These findings suggest that glucose ingestion appears to preferentially affect the performance of mice with worse glucose regulation. Similar findings were also observed in early human studies evaluating the effects of glucose ingestion on the cognitive performance of young and older adults with varying levels of evoked glucose (Allen, Gross, Aloia, & Billingsley, 1996; S. Craft, Murphy, & Wemstrom, 1994; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; C A Manning, Hall, & Gold, 1990; Messier, 1997; Messier, Desrochers, & Gagnon, 1999). Taken together, the results suggest that locally, glucose supply may not be optimal under conditions of increased neuronal activity and that peripheral glucose increases may selectively raise extracellular brain glucose levels in these regions. The rate of glucose utilization or glucoregulation, therefore, appears to have implications for overall neuropsychological processing. Given that the prevalence of type II diabetes and glucose intolerance in young adults is on the rise (Hoffman & Armstrong, 1996; McCance et al., 1994; Pinhas-Hamiel et al., 1996), an examination of the impact of poor glucose regulation on brain functions in such populations appears of importance. The purpose of the present study is to evaluate

neuropsychological function associated with glucose regulation in young human participants.

In the next few paragraphs, some of the key concepts and processes associated with glucose regulation will be defined. An extreme glucoregulatory condition in which the neuropsychological effects of glucose regulation can be observed is diabetes mellitus. This condition results from either the absence or ineffective use of insulin. There are two general types of diabetes mellitus: juvenile-onset insulin-dependent diabetes mellitus (type 1 diabetes) and maturity-onset non-insulin-dependent diabetes (type 2 diabetes). Normal glucose tolerance is defined as fasting glucose concentrations below 6.1 mmol/L and 2-hour post-load glucose concentrations below 7.8 mmol/L using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water; Impaired fasting glucose (IFG) is defined as fasting glucose concentration between 5.6 and 6.9 mmol/L; Impaired glucose tolerance is defined as fasting glucose concentration below 7.0 mmol/L and 2-hour post-load glucose concentrations between 7.8 and 11.1 mmol/L; Diabetes is defined as fasting glucose concentration above 7.0 mmol/L, casual glucose concentrations above 11.1 with diabetes symptoms, or 2-hour post-load concentration above 11.1 mmol/L (American Diabetes Association, 2002, 2006). In both types of diabetes, the aim of treatment is to maintain normal glucose levels and utilization in order to prevent neurological complications such as retinopathy, nephropathy, and neuropathy that may result from hypo- and hyperglycemia.

Type I diabetes, formally also known as insulin-dependent diabetes mellitus (IDDM), is the more serious form and is usually manifested in childhood or in young adulthood. Individuals with type 1 diabetes are eventually unable to secrete insulin

because of progressive damage from cellular-mediated auto-immune destruction of the insulin-producing beta cells of the pancreas (Atkinson & Maclaren, 1994). It has been demonstrated that the auto-immune destruction of beta-cells has been linked to multiple genetic predispositions as well as to environmental factors (American Diabetes Association, 2002). Although not incompatible, obesity is rare in this form of diabetes. Type I diabetes patients depend on insulin injections for survival and this results in substantial fluctuation of glucose concentrations in response to food ingestion, exercise and the insulin injections themselves.

Type II diabetes, formally also known as noninsulin-dependent diabetes mellitus (NIDDM) differs from type I diabetes in that type II diabetes is not characterized by auto-immune destruction of the insulin-producing beta cells. Type II diabetes patients are able to produce insulin, however, the disease is characterized by slower glucose absorption by insulin-sensitive cells and higher fasting glucose levels that result from factors such as reduced hepatic insulin sensitivity, reduced insulin secretion and increased glucagons secretion (Kahn, 1994). As a result, the metabolic disturbances observed in type 2 diabetes are less pronounced than in type 1 diabetes. Initially, compensatory hyperinsulinemia to maintain normal glucose concentrations is observed. This increase in insulin appears to overcome the defect in insulin action. When individuals are no longer able to sustain hyperinsulinemia, hyperglycemia appears to develop (G. M. Reaven, 1993). At this point, overt type 2 diabetes is observed and is characterized by a relative decrease in insulin secretion (Kumari, Brunner, & Fuhrer, 2000). Insulin resistance has been associated with microvascular angina, an increase in Plasminogen activator inhibitor-1, hyperuricemia, high blood pressure, cerebrovascular disease,

coronary heart disease. The latter has been linked to high levels of plasma triglycerides, low levels of HDL-cholesterol, and high levels of LDL-cholesterol (G. M. Reaven, 1993).

Patients with type 2 diabetes are initially treated with dietary restrictions and exercise to control for hyperglycemia. If or when hyperglycemic control is not achieved, patients are then prescribed oral hypoglycaemic agents to further control hyperglycemia. A final treatment for type 2 diabetes, when hypoglycaemic agents become no longer effective in maintaining euglycemia, consists of daily insulin injections. The risk of developing type 2 diabetes increases with age, obesity or increased percentage of body fat distributed predominantly in the abdominal region, and lack of physical activity (American Diabetes Association, 2002). Type 2 diabetes is characterized by a strong genetic predisposition, stronger than type 1 diabetes, however the genetics are complex (American Diabetes Association, 2002). This form of diabetes could remain undiagnosed for many years because initial symptoms of hyperglycemia are not severe enough for patients to notice and they are at higher risk of developing macrovascular and microvascular complications (Kuusisto, Mykkanen, Pyorala, & Laakso, 1994; Uusitupaa, Niskanen, Siitonen, Voutilainen, & Pyorala, 1993).

In the following sections, a review of the research evaluating the effects of diabetes (type 1 and type 2) on cognition will be presented as this research examined the the impact of the more extreme cases of impaired glucose regulation on neuropsychological function.

Neuropsychological Performance of Patients with Type 1 Diabetes

can be attributed to glucose fluctuations. One early study compared the performance of 40 adolescents with type 1 diabetes, who had developed diabetes between the ages of 5 and 12 to 40 demographically similar nondiabetics on measures of verbal intelligence, visuomotor coordination, and critical flicker threshold (C Ryan, Vega, Longstreet, & Drash, 1984). Although diabetic subjects performed within normal limits on all tests, significant group differences were observed on these three general measures. The authors did not attribute the poor performance on the visuomotor and flicker tasks to peripheral neuropathy or retinopathy for no participant showed clinical evidence of neuropathy and only 3 showed evidence of early retinal changes.

In another study, 37 young adults with type 1 diabetes were compared to 26 nondiabetic participants on a variety of cognitive tests (Franceschi et al., 1984). Although no differences were observed on intelligence, concentration and attention, spatial, visual, and psychomotor tests, the diabetic group performed significantly worse in global memory, abstract reasoning, and eye-hand coordination tests. Given that neither background retinopathy nor mild peripheral neuropathy predicted neuropsychological performances, the authors concluded, as had Ryan, Vega, Longstreet, and Drash (1984), that performance differences were not attributable to neurological damage. Furthermore, neither study found significant correlations between duration of disease and test performance and neither reported metabolic control nor age of onset as a predictive factor of neuropsychological performance.

Metabolic control as assessed by glycosylated hemoglobin (HgA_{1c}), which reflects metabolic control during the previous 2 to 3 months (Goldstein et al., 1995), is an important indication of the current extent of hypo- and hyperglycemia. In one study,

Metabolic control as assessed by glycosylated hemoglobin (HgA_{1c}), which reflects metabolic control during the previous 2 to 3 months (Goldstein et al., 1995), is an important indication of the current extent of hypo- and hyperglycemia. In one study, metabolic control was evaluated in 27 young adult men with type 1 diabetes (Holmes, 1986). Performance on intelligence, academic achievement, sensory and motor, and reaction time measures was compared between two diabetic subgroups: Good (HgA_{1c} < 11.0%) and Poor (HgA_{1c} > 11.0%) metabolic control. Men with poor metabolic control obtained lower scores on the Information and Vocabulary subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R;(Wechsler, 1981) and evidenced disrupted attention on a simple reaction time measure.

Evaluation of metabolic control in young men with type 1 diabetes was extended to determine cross-modal performance on reaction time and motoric tasks (Holmes, Tsalikian, & Yamada, 1988). The authors compared 6 diabetes patients with moderate (HgA_{1c} > 8.7 %) and 10 diabetes patients with near-normal (HgA_{1c} < 8.7%) blood glucose control. Contrary to what was expected, patients with near-normal blood glucose control demonstrated decreased attention on visual and auditory simple reaction-time tests. The groups, however, were comparable in their decision-making and motor skill performance. The findings of studies evaluating neuropsychological effects of metabolic control in type I diabetes patients are not entirely consistent. It is possible that methodological differences, including demographic, severity of type 1 diabetes or differences in test sensitivities could account for such differences. It is also possible that other factors may be interacting with metabolic control and contributing to this variability.

A recent meta-analysis (Brands, Jan Biessels, De Haan, Kappelle, & Kessels, 2005) evaluated the effects of type I diabetes on cognitive function across 33 studies revealed a modest but significant difference in mental speed and mental flexibility between type I diabetes patients and healthy controls. Specifically, type I diabetes patients showed diminished intellectual abilities that did not appear to be attributed to level of education, metabolic control, or disease duration. However, the authors concluded that the majority of the Type I diabetes studies were small cross-sectional retrospective studies that did not appear to have sufficient power to investigate the independent effects of specific disease variables. They highlighted that longitudinal designs, rather, would be most effective at evaluating these variables and ensuring appropriate methodological control (e.g., control for level of education, socioeconomic background, and genetic factors). Nevertheless, some studies specifically evaluated disease variables associated with type 1 diabetes and are summarized below.

Effects of hypoglycaemic episodes on cognitive function of type 1 diabetes.

One interpretation that could account for the variability in the neuropsychological performance of type I diabetes patients was suggested by Holmes, Tsalikian, and Yamada (1988). They hypothesized that the number of hypoglycaemic episodes might have contributed to their counter-intuitive results: Diabetes patients in the near-normal metabolic control group had experienced more episodes of hypoglycaemic unconsciousness than did diabetes patients in the moderate metabolic control group (3.6 versus 0.3, respectively). Additional studies have also been conducted to evaluate the effects of hypoglycaemic episodes on neuropsychological performance type 1 diabetes.

In one study, performance of 100 middle-aged patients with type 1 diabetes was compared to performance of 100 healthy controls to determine whether these two groups differ in their IQ scores (Deary et al., 1993). The diabetic group did indeed have lower WAIS-R performance and Verbal IQ scores (Wechsler, 1981) than the control group, however, when frequency of severe hypoglycemia was controlled, the difference in performance IQ between the two groups was abolished. This finding was consistent with a previous study in which two middle-aged diabetic groups were compared: Type I diabetic patients with a history of recurrent and severe hypoglycemia and type I diabetic patients with no severe hypoglycemia (Wredling, Levander, Adamson, & Lins, 1990). The authors found that the hypoglycaemic group scored lower in tests of motor ability, short-term and associative memory and visuospatial tasks. They suggested two interpretations for their findings; either the cognitive impairment reflects a selection factor or that the recurrent episodes of severe hypoglycemia result in permanent cognitive impairment.

More recently, another study compared the performance of young adult type 1 diabetes patients with previous hypoglycaemic episodes to the performance of young adult type 1 diabetes patients with no history of hypoglycaemic episodes and to the performance of age-matched controls (Hershey, Craft, Bhargava, & White, 1997). Hershey et al., (1997) observed that type 1 diabetes patients with previous hypoglycaemic episodes performed worse on tasks assessing delayed recall of verbal information and on a vocabulary task compared to type 1 diabetes patients with no history of hypoglycaemic episodes and to age-matched controls. Both type 1 diabetes groups performed worse on verbal fluency and on a task requiring the identification of degraded pictures compared to

controls. The authors also described that the differences between these groups were more readily observed on declarative memory tasks associated with medial temporal lobe structures and described that these findings were in line with the observed deleterious effects of hypoglycemia on medial temporal lobe structures.

Decrements in performance on tasks associated with medial temporal lobe structures were also reported in another recent study evaluating hypoglycemic effects in children with type 1 diabetes (Hershey, Bhargava, Sadler, White, & Craft, 1999). Performance of children who had been randomly assigned to intensive diabetes therapy (IT) was compared to performance of children who had been randomly assigned to conventional diabetes therapy (CT) and to performance of nondiabetic controls. The evaluation encompassed verbal and nonverbal memory performance as well as motoric speed and response inhibition tasks. IT was associated with greater risk of hypoglycemia and children in this group performed worse on tasks of declarative spatial memory compared to children in the CT and nondiabetic control groups. Both groups of type 1 diabetes children were impaired on a fine motor control and speed task.

Taken together, these findings evaluating hypoglycaemic effects on neuropsychological performance of type I diabetes patients demonstrate that the number of hypoglycaemic episodes appears to be an important determinant of cognitive impairment, and is interacting with this population's cognitive performance.

Effects of age of onset of type 1 diabetes on cognitive function.

Another factor that may be interacting with the neuropsychological performance of type I diabetes patients is age of onset. Holmes (1986) observed that this factor was also associated with lower abstract reasoning performance in her sample of type I

diabetes patients. The findings evaluating the effects of age of onset on cognitive performance of type I diabetes patients suggest that early onset (before age 5) of type 1 diabetes is related to poorer short-term memory performance (Wolters, Yu, Hagen, & Kail, 1996), lower scores on the abstract/visual reasoning scale (Golden et al., 1989), and poorer generalized performance on tests such as intelligence, school achievement, visuospatial, memory, motor speed, and eye-hand coordination (C Ryan, Vega, & Drash, 1985) in comparison to age-matched diabetes patients with a later onset (after age 5) of type 1 diabetes. The differences in performance between early onset and late onset type I diabetes patients have been attributed to hypoglycaemic seizures or coma and to the sensitivity of children's central nervous systems (C M Ryan, 1988). Ryan described that the young child with diabetes has a greatly increased incidence of hypoglycaemic seizures or coma (Ternand, Go, Gerich, & Haymond, 1982) perhaps because of heightened responsiveness to insulin and that the brain of the young child is unusually sensitive to the effects of virtually any abnormal metabolic or electrophysiological event.

Effects of induced hypoglycaemia on cognitive function of type 1 diabetes.

History of hypoglycemic episodes has been shown to impede neuropsychological performance of type 1 diabetes patients. In addition, studies evaluating the effects of an induced hypoglycaemic state also appear to temporarily disrupt neuropsychological test performance in these patients. More specifically, it has been reported that attention and fine motor skills, as assessed by visual reaction time and time required to solve simple addition problems, was increased during hypoglycemia (Holmes, Hayford, Gonzalez, & Weydert, 1983). Verbal fluency and naming performance also appear to be disrupted during induced hypoglycaemic states (Holmes, Koepke, Thompson, Gyves, & Weydert,

1984). Furthermore, it has also been demonstrated that neuropsychological performance improves when hypoglycaemic states were reversed (Pramming, Thorsteinsson, Thielgaard, Pinner, & Binder, 1986). This finding demonstrates that the performance decrements resulting from an induced hypoglycaemic state are likely due to temporary neurological dysfunction.

Given that age of onset and/or hypoglycaemic episodes appear to interact with neuropsychological performance of type 1 diabetes, it is difficult to dissociate the specific effects of impaired glucose utilization on cognitive function from the complications arising from neurological damage caused by hypoglycaemic episodes. In type 2 diabetes, hypoglycemic events are generally rare, therefore, the effects of impaired glucose regulation can be more readily observed.

Neuropsychological Performance of Patients with Type 2 Diabetes

Numerous studies have been conducted to evaluate the neuropsychological functioning of individuals diagnosed with Type II diabetes. These investigations differ in the demographics of samples employed (age, gender, and duration of diabetes), in methodological control as well as in the neuropsychological test performances evaluated rendering cross-study comparisons difficult. Furthermore, studies evaluating the cognitive effects of type II diabetes have included cross-sectional, population, and longitudinal designs. Given the heterogeneity among studies, two tables summarizing the methodology and results of cross-sectional and population studies will be used to integrate findings and draw commonalities (see Appendix A for tables summarizing studies evaluating cognitive function of type 2 diabetes). In the next few paragraphs, the

general procedures and abbreviations/symbols used to compare these studies and evaluate the results will be presented.

The summary tables for the type 2 diabetes studies include information on demographics (number of participants and gender distribution, age, and education), diabetes (duration of diabetes, treatment modality, HbA percent, and fasting glucose levels), exclusion criteria (neurological conditions, psychiatric conditions, depressive symptomatology, the use of psychoactive medication, substance use, blood pressure, and cardiovascular and cerebrovascular disease risk factors) as well as information on statistical/methodological control of premorbid cognitive function or education. Information presented on exclusion criteria and statistical/methodological control indicate whether variables were matched or statistically adjusted or whether a given factor was used as an exclusion criterion for the study (X), as well as whether differences between groups were observed using ``>`` or ``<`` signs to indicate statistically significant differences ($p < .05$).

The results of the studies were identified in columns reflecting the nature of the measures used and are more specific than what has been previously presented (Stewart & Liolitsa, 1999; Strachan, Deary, Ewing, & Frier, 1997) to allow for analysis of sensitivity of each measure. They encompass Lezak's classification of cognitive abilities, which include the following: verbal memory, visuospatial memory, attention, psychomotor/performance IQ, frontal lobe/executive function, and Mini-Mental State Examination (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004; Strachan, Deary, Ewing, & Frier, 1997). Brief screening measures of cognitive function were also included (e.g., MMSE; (Folstein, Folstein, & McHugh, 1975); Telephone Interview for

Cognitive Status, (Brandt, Spencer, & Folstein, 1988) as well as measures evaluating overall cognition, memory, attention, vocabulary (e.g., Vocabulary subtest of WAIS-R) or long-term semantic knowledge (e.g., Information of WAIS-R) and language abilities, which were identified independently.

The results were reported using an effect size estimate, Cohen's *d* (Cohen, 1988), and statistically significant group differences ($p < .05$) were identified (*) to provide a comprehensive overview of the strength of findings. Positive effect sizes reflect poorer performance of type 2 diabetes group compared to performance of the control group whereas negative effect sizes reflect the contrary (poorer performance of the control group compared to the type 2 diabetes group). In cases where other statistical analyses were used (e.g., regression or factor analyses) and performance means and variances were not reported, measures that were evaluated were identified by an "E" and statistically significant comparisons were identified by "E*". For studies that have employed more than one test to assess a given cognitive function, the number of tests employed is indicated by the number of "Es" assigned to the given column. Furthermore, for population studies, odds ratio (OR) estimates were also provided with 95% confidence intervals, when available, as estimates of the likelihood of poorer performance of type 2 diabetes patients compared to controls on the given measures.

An examination of statistically significant findings reveals no direct relationship between sample size, education level, or age of type 2 diabetes patients and statistically significant differences in performance between type 2 diabetes and control groups. This suggests that differences in performance between type 2 diabetes patients and controls do not appear to be explained by differences in sample size, educational level or age of the

participants recruited in the studies. This lack of differences in demographics is supported by findings of prospective studies that demonstrated that individuals with type 2 diabetes showed a decline in cognitive abilities over time, despite intact abilities at baseline assessments (Hassing, Grant et al., 2004; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004).

Nevertheless, the findings reveal no consistent neuropsychological decrement among studies. Furthermore, the proportion of significant performance differences between type 2 diabetes patients and controls relative to nonsignificant differences across all measures is low (approximately 25%). Despite the variability in performance, the general conclusions will be presented in the next few paragraphs.

To begin with, the cross-sectional studies evaluating cognitive function of treated type 2 diabetes patients demonstrate that relatively larger effect sizes and more statistically significant differences between diabetes patients and controls were reported on measures of immediate noncontextual verbal memory as well as on processing speed and brief cognitive screening measures (e.g., MMSE; (Folstein, Folstein, & McHugh, 1975) compared to other measures evaluated. A smaller proportion of studies have also found some differences on measures of immediate and delayed contextual verbal memory, delayed noncontextual verbal memory, nonverbal immediate and delayed memory, arithmetic, letter fluency, as well as on specific neuropsychological tests including Digit-Symbol Coding (WAIS-R; (Wechsler, 1981), Trails A and B (Spreen & Strauss, 1991), Stroop color, word and interference (Spreen & Strauss, 1991), and Wisconsin Card Sorting (Berg, 1948). Finally, the cross-sectional studies demonstrate that it is less likely to observe statistically significant differences on measures of

visuospatial function (none of the 19 differences were statistically significant and most effect sizes were small), verbal recognition, abstract conceptualization tasks (e.g., Similarities subtest of the WAIS-R), verbal and nonverbal reasoning (e.g., Comprehension of the WAIS-R), long-term semantic knowledge, language abilities, working memory tasks, categorical fluency tasks as well as on specific neuropsychological measures including Digit Span (WAIS-R) and Block Span (E. Kaplan, Fein, Morris, & Delis, 1991).

The findings of the population studies demonstrate that treated type 2 diabetes patients are more likely to show poorer performance on brief cognitive screening measures. Measures of immediate and delayed contextual verbal memory, immediate noncontextual verbal memory, nonverbal immediate and delayed memory, visuospatial processing, processing speed/reaction time, letter and categorical fluency, abstract conceptualization, long-term semantic knowledge, and language abilities as well as specific neuropsychological measures including Digit Span Forward and Backward (Wechsler, 1981), and Trails A and B (Spreen & Strauss, 1991), were less likely to show significant differences, medium-large effect sizes or odds ratios. Given that a smaller number of cognitive measures were evaluated in population studies relative to measures used in the cross-sectional studies and their poorer sensitivity to mild cognitive impairment (e.g., MMSE; (Folstein, Folstein, & McHugh, 1975; Galasko et al., 1990), conclusions from population studies are tentative.

In conclusion, the results of cross-sectional and population studies demonstrate that even among well-controlled studies, findings across all neuropsychological measures evaluated are inconsistent. Most sensitive measures of performance decrements of

treated type 2 diabetes patients include measures of immediate noncontextual verbal memory such as word list recall, as well as processing speed/reaction time and brief cognitive screening measures (e.g., MMSE; (Folstein, Folstein, & McHugh, 1975). Measures that are less likely to show significant differences between type 2 diabetes patients and controls include measures of visuospatial processing, measures of auditory or visual attention as well as measures of long-term semantic knowledge and language abilities. All other measures of cognitive function, including measures of executive function, and nonverbal memory have shown inconsistent findings. As Stewart and Liolitsa (1999) concluded, variability in findings could be accounted for by differences in methodology across studies which could include inadequate sample sizes or group matching as well as differing test sensitivities. An important consideration highlighted by Stewart and Liolitsa is the extent to which cognitive impairment associated with diabetes reflects small effects across most subjects versus large effects within a highrisk subgroup. More specifically, it is to be determined whether the differences observed reflect significant cognitive dysfunction among a diabetic subgroup due to complicating factors such as cerebrovascular disease or whether the overall differences reflect consistent minor decrements among most treated patient with type 2 diabetes.

In the following section, the role of factors that appear to mediate or interact with the cognitive performance of type 2 diabetes patients will be discussed in order to determine the independent effects of glucose regulation on cognitive function. These include glucoregulatory control and cardio- and cerebro-vascular risk factors.

<u>The effects of glucoregulatory control and vascular risk factors on the cognitive function of type 2 diabetes.</u>

The effects of glucoregulatory control on the cognitive function of type 2 diabetes patients can be evaluated by examining studies that investigated the effects of diabetes treatment on cognition. The use of a given treatment reflects glucoregulatory control: patients requiring insulin for glycemic control are at the most severe stage of glucose regulation compared to patients treated with lifestyle changes (diet and exercise) or hypoglycaemic agents. In addition, as described above, insulin treatment could result in hyper- and/or hypo-glycemic episodes, which could adversely affect cognitive function.

Several studies have evaluated performance differences between type 2 diabetes patients being treated with insulin, patients treated with oral hypoglycaemics and patients treated with diet alone. The findings demonstrated that type 2 diabetes patients requiring insulin treatment were at a higher risk of performing worse or were more likely to show cognitive decrements than type 2 diabetes patients requiring either oral hypoglycaemic agents or diet (P. K. Elias et al., 1997; Gregg et al., 2000; Jagusch, v. Cramon, & Hepp, 1992; Mogi et al., 2004).

This observation, however, was not replicated in two other cross-sectional studies (Soininen, Puranen, Helkala, Laakso, & Riekkinen, 1992; Wahlin, Nilsson, & Fastbom, 2002). This inconsistency could be attributed to relatively small sample sizes of type 2 diabetes patients requiring insulin treatment (n=2) in the Wahlin et al., study and to more limited cognitive assessments conducted. Furthermore, given that Soininen et al., compared treatment effects between type 2 diabetes patients requiring drugs (n=11 for oral hypoglycaemic agents; n=1 for insulin) and type 2 diabetes patients treated with diet (n=13), it is possible that the potential effects of severity of type 2 diabetes on cognitive function only be observed in patients requiring insulin treatment.

Taken together, the findings of studies evaluating treatment needs in type 2 diabetes, suggest that patients requiring a more significant regulation of glycemic levels (i.e, requiring insulin treatment) and possibly, more severe diabetes, are more likely to show decrements in cognitive performance compared to type 2 diabetes patients at a relatively earlier stage of treatment (i.e., requiring oral hypoglycaemic agents or diet).

Another line of investigation supporting the view that glucoregulatory control is related to cognitive performance stems from studies evaluating the neuropsychological performance of nondiabetic adults who show impaired glucose tolerance. Protracted glucose tolerance impairment usually precedes a type 2 diabetes diagnosis. In a longitudinal study evaluating the development of type 2 diabetes, the diagnosis of type 2 diabetes was preceded by 5 years of elevated 2-hour insulin levels and approximately 2.5 years of elevated 2-hour glucose levels (Hara, Egusa, & Yamakido, 1996). Given that considerable variability in glycemic control is observed in pre-diabetic individuals, several studies have evaluated the neuropsychological function of these individuals. The following section provides a review of this literature.

Effects of impaired glucose tolerance (World Health Organization).

The relationship of cognitive function, assessed by the MMSE, to diabetes, impaired glucose tolerance and hyperinsulinemia as well as the role of factors potentially mediating decrements in cognitive performance (e.g., cardiovascular disease and other risk factors associated with insulin resistance) was evaluated in a population-based cohort of 462 men (mean age: 75 ± 4.6 years; (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995). Type 2 diabetes, impaired glucose tolerance, and control participants were classified according to the World Health Organization (World Health Organization,

1985) guidelines utilizing fasting, and 2-hour plasma glucose concentrations following a glucose load of 75g. for the classifications. Hyperinsulinemia in this study was assessed using comparisons of quartile groups divided according to the distribution of the area under the insulin curve. Fasting, 1-hour and 2-hour insulin values post-glucose load were used to compute the area under the curve. The factors evaluated to assess the effects of potential mediators of cognitive dysfunction in the study included: cigarette smoking, BMI, HDL cholesterol, triglycerides, fibrinogen, stoke, transient ischaemic attack, myocardial infaction, angina pectoris, intermittent claudication, and hypertension. The findings of this study demonstrated that subjects classified as having impaired glucose tolerance or as having hyperinsulinemia were associated with impaired MMSE (Folstein, Folstein, & McHugh, 1975) performance. Performance of type 2 diabetes patients was even more impaired and decreased with increasing levels of fasting glucose. The authors also demonstrated that hyperinsulinemia as well as type 2 diabetes and impaired glucose tolerance were associated with impaired performance independent of fasting insulin. Furthermore, these relationships were unchanged when the potential mediating factors were taken into account.

Impaired glucose tolerance was also evaluated in another population-based sample, however, using more sensitive neuropsychological measures of cognitive function (Vanhanen et al., 1998). The WHO guidelines were also used to classify 506 subjects (mean age: 73.3 ± 2.9) as having normal glucose tolerance and 80 (mean age: 72.9 ± 3.0) as having impaired glucose tolerance. Participants' MMSE (Folstein, Folstein, & McHugh, 1975) performance, verbal and visual memory, Trail-making performance (Spreen & Strauss, 1991), as well as Category and Letter Fluency were

evaluated. The groups were also compared on health risk factors: Total cholesterol, HDL cholesterol, total triglycerides, systolic and diastolic blood pressures, BMI, alcohol and cigarette consumption, self-reported depression, history of hypertension, angina pectoris, myocardial infarction and cerebral infarction. The impaired glucose tolerance group showed higher HDL and total triglycerides levels, systolic and diastolic blood pressure, as well as BMI and were more likely to have a history of hypertension. The performance of the two groups revealed a trend for lower scores on all tests for the impaired glucose tolerance group. Only performance on the long-term verbal memory task and MMSE were statistically different between the two groups. Furthermore, performance comparisons between males and females within each group demonstrated that males with impaired glucose tolerance were significantly worse than males with normal glucose tolerance and both groups of females. The authors also ran a multiple stepwise linear regression using age, education, sex, hypertension, 2-hour glucose and insulin to predict performance on the MMSE. The results of these analyses revealed that whereas age and education were associated with MMSE scores in the normal glucose tolerance group, age, education and 2-hour insulin levels were associated with MMSE scores in the impaired glucose tolerance group.

In another recent study, however, the decrements in cognitive function were not associated with impaired glucose tolerance (Lindeman et al., 2001). Lindemann et al., (2001) compared 188 type 2 diabetes patients to 175 impaired glucose tolerance patients and 476 normal glucose tolerance participants on measures of attention, memory, visuospatial functioning and cognitive flexibility. They observed that the type 2 diabetes and impaired glucose tolerance patients were comparable to the normal glucose tolerance

participants on all measures except for the visuospatial measure (pentagon drawing) on which the impaired glucose tolerance group demonstrated superior performance compared to the other two groups. The findings of this study are difficult to interpret for the three groups were differentially treated: the impaired glucose tolerance and normal glucose tolerance groups and only half of the type 2 diabetes group (not previously diagnosed diabetes patients) ingested 75g of glucose prior to assessment. Glucose ingestion has been shown to differentially affect cognitive performance depending on glucoregulatory status (S. Craft, Murphy, & Wemstrom, 1994; R T Donohoe & Benton, 2000; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997), therefore, glucose may have improved the cognitive performance in the impaired glucose tolerance group and possibly the diabetes group which would have reduced the differences between these groups and the normal control group.

In another study, cognitive performance of type 2 diabetes patients (n = 26) was compared to the performance of normoglycaemic older adults with increased risk for developing type 2 diabetes (n = 22) and to the performance of normoglycaemic older adults with low risk for developing type 2 diabetes (n = 26;(Vanhanen et al., 1997). The risk groups were classified using median 2-hour glucose and insulin plasma levels following a 75g glucose load: Low risk participants showed glucose and insulin levels below 5.9 mmol/l and 279.6 pmol/l, respectively, and high risk participants showed levels above these medians. Using age, education, and sex as covariates, type 2 diabetes patients were impaired on a verbal and visual memory task, the Stroop (color) test (Spreen & Strauss, 1991), and the Digit Symbol test (Wechsler, 1981) compared to the

low risk group. The high-risk participants also showed decrements on these tasks as well as on a verbal fluency task. Furthermore, type 2 diabetes and high-risk participants were comparable on all measures evaluated. The authors attributed the performance decrements of the high-risk group to hyperinsulinemia as reflected by participant's elevated insulin levels and BMI. More recently, findings from a 4-year prospective study (Yaffe et al., 2004) revealed that women with impaired fasting glucose (n = 297; mean age = 68 years) also showed worse performance on measures of processing speed, memory, and the composite scores (also included fluency and divided attention) relative to controls (n = 6463, mean age = 66 years) but that their performance was better than that of women with diabetes (n = 267; mean age = 68 years). The findings also revealed greater odds (almost twofold increase) of cognitive decline over the 4-year period.

In summary, the findings of studies evaluating cognitive performance of nondiabetic participants with evidence of impaired glucose regulation or impaired fasting glucose demonstrate that decrements in cognitive performance associated with glucoregulatory control can be observed independent of a type 2 diabetes diagnosis. This effect is more readily observed for verbal memory processes. The findings also demonstrate that insulin levels, independent of glucose levels, also appear to be associated with decrements in performance of nondiabetic adults. These decrements do not appear to be due to risk factors associated with hyperinsulinemia (i.e., cardio and cerebrovascular disease). These conclusions are also supported by studies that examined the impact of glycemic control improvement on cognitive performance in type 2 diabetes participants (Gradman, Laws, Thompson, & Reaven, 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993; Naor M, Steingruber HJ, Westhoff K, Schottenfeld-Naor Y, &

AF, 1997; CM Ryan et al., 2006; Wu et al., 2003), which demonstrated that decrements in performance are dependent on transient glycemic control in type 2 diabetes rather than the complications associated with type 2 diabetes. This finding also suggests that more consistent decrements in type 2 diabetes patients would likely be observed if performance comparisons were conducted between untreated type 2 diabetes patients with controls to control for the effects of diabetes treatment.

Effects of cardiovascular factors on cognitive function of type 2 diabetes patients.

Given that cardiovascular and cerebrovascular disease factors are associated with type 2 diabetes (Biessels, 1999; Kumari, Brunner, & Fuhrer, 2000; G. M. Reaven, 1993; R Schmidt et al., 2004; Strachan, Deary, Ewing, & Frier, 1997; Vanhanen et al., 1997; Vanhanen et al., 1999) and that these factors independently have been shown to be associated with decrements in cognitive performance(Desmond, Tatemichi, Paik, & Stern, 1993; M. F. Elias, Wolf, D'Agostino, Cobb, & White, 1993; Kilander, Nyman, Boberg, & Lithell, 1997; Kumari, Brunner, & Fuhrer, 2000; Lopez et al., 2003; Nilsson, Fastbom, & Wahlin, 2002; Prencipe et al., 2003; Vanhanen et al., 1999; Verhaeghen, Borchelt, & Smith, 2003; Zaslavsky, Gross, Chaves, & Machado, 1995), several studies have evaluated the effects of cardiovascular and cerebrovascular risk factors on cognitive function in type 2 diabetes to determine the extent of its effects. In one well-controlled population study, Elias et al. (1997) evaluated the effects of hypertension as a risk factor of cardiovascular disease on the performance of type 2 diabetes participants. They reported an interaction between type 2 diabetes and hypertension on cognitive performance, which was associated with greater risk of poor performance on tests of visual reproduction (assessing visual memory) and on the composite score which

included performance on verbal and visual memory tasks as well as on simple auditory attention, abstract reasoning and verbal fluency measures. This finding, however, was not replicated in two longitudinal studies (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Gregg et al., 2000) that also examined the interacting effect of hypertension on the performance of type 2 diabetes patients (mean ages 72 years and 65 years, respectively). Another recent longitudinal study demonstrated that although participants with either diabetes, hypertension, or both diabetes and hypertension, showed comparable performance on a cognitive screening measure at baseline (mean age = 83 years), participants with both diabetes and hypertension showed the greatest decline over an 8-year period relative to the other groups (Hassing, Hofer et al., 2004). Thus, it appears that long-term follow-up into older age ranges and/or allowing for longer disease durations might be necessary to determine the interactive effects of hypertension. Given that only few studies evaluated the interacting effect of hypertension, it is possible that the inconsistent findings be attributed to differences in the neuropsychological measures used. It is also possible that hypertension does interact with type 2 diabetes performance, however, given that type 2 diabetes decrements are mild as are decrements associated with hypertension, interacting effects might be more difficult to observe.

Other studies have evaluated the interacting effects of cardiovascular and cerebrovascular risk factors such as history of stroke, or heart disease and suggest that these risk factors do not interact with the cognitive decrements associated with type 2 diabetes (Nilsson, Fastbom, & Wahlin, 2002; G M Reaven, Thompson, Nahum, & Haskins, 1990; Wahlin, Nilsson, & Fastbom, 2002; Worrall, Moulton, & Briffett, 1993; Zaslavsky, Gross, Chaves, & Machado, 1995). A small cross-sectional study that

conducted a comprehensive neuropsychological assessment and used other measures of cardiovascular and cerebrovascular risk factors (serum total and very-low-density lipoprotein triglycerides, systolic blood pressure and body mass index), however, demonstrated that serum total and very-low-density lipoprotein triglycerides were negatively related to verbal fluency in type 2 diabetes patients (Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995). No relationship between these factors and performance of controls was observed. This finding was also replicated by another cross-sectional study, (Jagusch, v. Cramon, & Hepp, 1992), which reported a negative correlation between fasting triglycerides and reaction time measures as well as between fasting cholesterol and auditory and visual attention in type 2 diabetes patients.

These studies used different procedures to assess for the various cardiovascular and cerebrovascular risk factors and cognitive function, rendering comparisons and conclusions difficult. Most studies have shown that cardiovascular and cerebrovascular risk factors do not appear to interact with type 2 diabetes performance. This conclusion is supported by the observation that brain atrophy is 40% more frequent in patients with diabetes than in controls (Araki Y et al., 1994) and that amygdala and hippocampus volumes are reduced in diabetes patients relative to controls, independent of vascular pathology (den Heijer et al., 2003; den Heijer T, 2003). Nevertheless, one well-controlled population study and one longitudinal study demonstrated that hypertension appears to further impede the cognitive performance of type 2 diabetes patients. Indeed, a recent magnetic resonance imaging study demonstrated cortical atrophy only in patients with both diabetes and hypertension (R. Schmidt et al., 2004), supporting the view that cardio- and cerebrovascular factors appear to contribute to some of the cognitive

dysfunction observed in type 2 diabetes patients. Furthermore, high levels of triglycerides have also independently shown to be related to decrements in type 2 diabetes performance. Additional replications are needed to further substantiate the effects of cardiovascular and cerebrovascular disease on the cognitive function of type 2 diabetes patients.

Another way to determine whether type 2 diabetes is associated with cognitive decrements is to evaluate the long-term effects of diabetes on cognitive function and whether changes over time are observable in repeated-measures designs. Longitudinal studies allow for this assessment and limit the between-subjects variability observed in cross-sectional studies.

Several recent longitudinal studies have been conducted to evaluate the relationship between cognitive decline and type 2 diabetes. In one study, the performance of 682 women with diabetes (mean duration of type 2 diabetes = 10.2 years; SD = 9.5 years) was compared to the performance of 8997 age-matched women (mean age = 72 years) who were assessed on two occasions: at baseline and 3 to 6 years following baseline assessment (Gregg et al., 2000). Variables such as age, education, depression, hypertension, and cardiovascular disease were methodologically controlled. Neuropsychological assessment included a modified version of the MMSE as a brief cognitive screening measure, a psychomotor speed test and a measure of frontal lobe/executive function. The results of this study reveal increased odds of major cognitive decline in type 2 diabetes patients (defined as the greatest 10^{th} percentile reduction in performance from initial to follow-up score) on the psychomotor speed test,

768 age-matched controls (mean age = 65 years) on several neuropsychological tests including the MMSE as well as measures of verbal and visual memory, facial recognition, executive function, motor function, arithmetic ability, processing speed and logical reasoning (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001). They controlled for age, gender, education, depression, hypertension and body mass index, however reported that diabetic participants had higher levels of triglycerides, and lower levels of total cholesterol and HDL cholesterol compared to controls. They concluded that the odds ratio for serious worsening in the diabetic group (defined as a change in scores into the worst 15% of the distribution of the observed changes for the whole sample) were greater than 2 for measures of verbal memory, facial recognition, processing speed and motor function when controlling for age, gender, education and systolic blood pressure.

These findings were supported by a more recent study (Logroscino, Kang, & Grodstein, 2004) which evaluated the performance of women (aged 70-81 years, n = 1394) over a two-year period on measures of overall cognitive function (TICS and a global composite score encompassing immediate and delayed verbal recalls, verbal fluency, and backward span). The findings revealed greater odds ratio of poor baseline score (below 10% of distribution) for women diagnosed with type 2 diabetes compared to women without diabetes. There was also evidence of higher odds ratios of poorer performance for women with untreated diabetes or longer duration of diabetes (> 15 years) compared to women without diabetes, and for women using insulin relative to women treated with oral medications or without diabetes. Cognitive decline was observed following only a two-year period with greater odds ratio of poorer performance on the TICS for women with type 2 diabetes compared to women without diabetes.

performance for women with untreated diabetes or longer duration of diabetes (> 15 years) compared to women without diabetes, and for women using insulin relative to women treated with oral medications or without diabetes. Cognitive decline was observed following only a two-year period with greater odds ratio of poorer performance on the TICS for women with type 2 diabetes compared to women without diabetes. Yaffe et al. (2004) also observed a similar finding in their 4-year prospective study on women (mean age = 66 years). Specifically, they found that women with type 2 diabetes had worse baseline scores on measures of processing speed, divided attention, verbal fluency, verbal memory and the composite score compared to controls and women with impaired fasting glucose. Furthermore, they showed an approximate twofold higher risk of developing dementia or cognitive impairment after four years. Taken together, the longitudinal studies to date suggest that the type 2 diabetes participants are at a higher risk of cognitive decline compared to age-matched controls.

The findings of these longitudinal studies are further substantiated by studies evaluating risk of co-existence of diabetes and dementia. Some studies evaluating the co-existence of these two diseases reported a moderate association between diabetes and Alzheimer's disease with odds ratios ranging from 1.3 to 1.9 (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Brayne et al., 1998; Ott et al., 1996; Ott et al., 1999; Peila, Rodriguez, & Launer, 2002; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004), with higher odds ratios (i.e., 2.6) for vascular dementia, particularly when diabetes occurred with severe systolic hypertension or heart disease. However, the association between dementia and diabetes has not been consistently observed as other studies did not report

an association (Odds ratio ranging from 1.0 to 1.3; (Curb et al., 1999; Leibson et al., 1997; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001).

More recently, it has been demonstrated that the odds ratio for the co-existence of diabetes and Alzheimer's disease significantly increased only for subjects with the ApoE4 allele (Lehtovirta M et al., 1995; Peila, Rodriguez, & Launer, 2002). Post-mortem examination of these subjects revealed that Alzheimer's patients who were diabetic had increased number of infarcts and that the ApoE4 allele was associated with increased neurofibrillary tangles in the hippocampus and cortex and increased cerebral amyloid angiopathy (Peila, Rodriguez, & Launer, 2002). Given several reports that Alzheimer's disease is associated with hyperinsulinemia (Bucht, Adolfsson, Lithner, & Winblad, 1983; S. Craft et al., 1993; S Craft et al., 1996; S. Craft et al., 1998; S. Craft & Watson, 2004; Luchsinger, Tang, Shea, & Mayeux, 2004; Steen E et al., 2005), the relationship between diabetes and Alzheimer's disease could be mediated by insulin-degrading enzyme, which also degrades beta-amyloid protein. Given that insulin competes with beta-amyloid for the insulin-degrading enzyme, it has been proposed that in some cases, Alzheimer's disease lesions could be increased by excessive levels of insulin because of high levels of beta-amyloid left undegraded. Other mechanisms that have also been proposed to account for the link between Alzheimer's disease and diabetes include decreased cortical glucose utilization in the hippocampus and entorhinal cortex, and increased oxidative stress subsequent to the formation of advanced glycation end-products (Grossman, 2003).

One study evaluating the co-existence of Alzheimer's disease with diabetes reported a strong association between Alzheimer's disease patients with cerebrovascular

disease and diabetes (odds ratio 3.0; (Ott et al., 1999). More specifically, the odds ratios of Alzheimer's disease with cerebrovascular disease and diabetes increased with diabetes treatment need: odds ratios of 1.3, 2.4, and 4.3 were observed for subjects with diabetes, treated with diet, hypoglyceamic agents and insulin, respectively. This finding is consistent with the strong association observed between vascular dementia and diabetes (Brayne et al., 1998; Leibson et al., 1997; Mortel, Wood, Pavol, Meyer, & Rexer, 1993; Ott et al., 1999; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004).

Taken together, research evaluating the cognitive function of type 2 diabetes suggests that initial decrements in performance appear to be attributed to reversible impaired glucoregulatory control and can be reversed by diabetic treatment. Studies evaluating the effects of confounding factors associated with type 2 diabetes (i.e., cardiovascular disease) as well as studies assessing risk of cognitive decline and dementia in type 2 diabetes patients suggest that over time, cognitive decrements in type 2 diabetes become irreversible, particularly if associated with the ApoE4 allele, and are likely attributed to prolonged hyperinsulinemia and/or vascular disease.

The main purpose of this study is to investigate the relationship between glucose regulation and cognition in young non-diabetic adults. As such, the following section will provide a review of the studies to date that have evaluated this relationship in both young and older adults with varying glucose regulation who, at the time of assessment, showed no evidence of diabetes. Given that hyperinsulinemia and associated vascular disease are less likely to be observed in these populations, assessment of cognitive function will more likely reveal the neuropsychological functions associated with glucose regulation.

Neuropsychological Performance of Nondiabetic Adults with Varying Glucose Regulation

Although glucose regulation involves multiple processes and is dependent on a number of factors, including insulin secretion and sensitivity, liver function, fat and muscle mass, the action of other regulatory hormones such as glucagons, gut hormones, neural stimulation and gastric emptying and absorption (Radziuk, 2000), the concept "glucose regulation" in studies of nondiabetic adults was used primarily to reflect the product of such processes, rather than the actual processes themselves. Thus, the concept of glucose regulation should only be interpreted as an *index* of the underlying mechanisms and processes associated with glycemic control. Furthemore, the effects of glucose ingestion on cognitive performance as well as how they relate to the performance of better and worse glucose regulators were also evaluated in most of these studies (see the following sections for a review of the underlying mechanisms involved in glucose-mediated cognitive enhancement). A summary of these studies is presented in Appendix B.

One of the first studies evaluating the effects of glucose regulation in nondiabetic adults used a counterbalanced cross-over design in which older (n = 11; mean age = 67.4 years) and younger (n = 12; mean age = 20 years) participants were tested over a 3-day period (J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989). Either glucose or saccharin was ingested following an overnight fast on the first two days. Participants were then administered a battery of tests modified from the WMS (Wechsler, 1945), separated by 15-minute intervals, in the following order: Paired-Associates of 10 word pairs; Logical Memory (immediate and delayed recall following a single presentation of

one story); Digit Span and Visual Reproduction (immediate recall following a 10-second presentation of each figure. Older participants were given a 30-minute break prior to the Digit Span and an additional beverage to maintain blood glucose levels. On the second day, participants were tested for the 24-hour recall of the Paired-Associates and then received the alternate test forms and solution. Finally, on the third day, the 24-hour recall of the Paired-Associates from day 2 was obtained.

The results demonstrated that in the young participants, glucose enhanced performance on the Digit Span (Forward) test and in the older participants, glucose enhanced performance of the Logical Memory test and the composite performance score. Their findings also indicated that in the older participants, peak increases from basal values in blood glucose levels (following ingestion of the glucose solution) inversely predicted logical memory and composite performance scores, independent of solution ingested and inversely predicted Visual Reproduction scores on the saccharin day. These results suggested that poorer glucose regulation was associated with poorer performance. Furthermore, performance of older participants with good glucose control (peak change < 100 mg/dl) was comparable to the performance of all younger participants on all measures. The authors concluded that brain glucose utilization is likely reduced in diabetes patients and in older adults reflecting the observed memory decrements, and that glucose administration may enhance glucose utilization and associated memory functions. Hall et al., also concluded that glucose regulation appears to be a marker of memory impairment regardless of the glucose level at the time of testing.

The relation between glucose regulation and memory performance in older individuals was also demonstrated in another study evaluating peak blood glucose values

using a repeated-measures counterbalanced design (C A Manning, Hall, & Gold, 1990). In this study, the performance of 17 older individuals (mean age = 73 years) on various tests assessing verbal and visual memory, attention, executive and motor function following ingestion of either a glucose or saccharin drink. To assess these functions, the following tests were administered in the following order: Ammons Quick test (requires the matching of words to pictures (Ammons & Ammons, 1962); Logical Memory (5-minute delayed recall following a single presentation of one story (Wechsler, 1981); Complex Figure Test (copy and immediate recall of figures (Osterreith, 1944); Selective Reminding Test (SRT; repeated list presentation of unrecalled words from a 12-word list until the correct recall of all 12 words or until 12 presentation trials; (Levin, Benton, & Grossman, 1982); Finger Oscillation Test (lever press using one finger from each hand (Reitan & Wolfson, 1985); Digit span test (Wechsler, 1945); Letter Cancellation Test (attention/motor task; (M. Lezak, 1983); and Logical Memory (40-minute delayed recall of the story). Their findings demonstrated that glucose only enhanced memory on the Logical memory at both recalls and on the SRT for the total number of words stored in long-term memory. Given that performance on these tests was not correlated, it was concluded that glucose has an effect on more than one aspect of declarative memory. More specifically, glucose appeared to have an effect on both contextual verbal (Logical Memory) and non-contextual verbal (SRT) tasks. In evaluating the effects of glucose regulation using peak glucose levels on both, glucose and saccharin days, the results demonstrated that glucose regulation was inversely related to the same tasks affected by glucose: SRT (long-term memory storage) and Logical Memory (both recalls) on the saccharin. Although the interaction between type of solution and glucose regulation was

not directly evaluated, the correlation patterns reflected that glucose appeared to attenuate the verbal memory decrements observed in those who showed worse glucose regulation.

Another study evaluated the effects of glucose regulation, determined by peak glucose levels, on the performance of a nonverbal memory test and nonmemory tasks in 28 older (mean age = 73 years) nondiabetic adults (Allen, Gross, Aloia, & Billingsley, 1996). A counterbalanced repeated-measures design was also conducted in which each subject was tested under both a glucose and saccharin condition. The following tests were administered: Complex Figure Test (copy and 20-minute delayed recall; (M. Lezak, 1983)); dichotic listening (immediate recall/repetition of two triads of words simultaneously presented to both ears on 11 trials (Spreen & Strauss, 1991); Trail Making (A and B; (Reitan, 1955); verbal fluency (Benton, 1968); Boston Naming Test (E. F. Kaplan, Goodglass, & Weintraub, 1978); Meier Visual Test (discrimination between four designs across 30 trials (Meier & French, 1965); Grooved Pegboard (fine-motor; (C. G. Matthews & Klove, 1964); and figural fluency (over 2 minutes using 3 lines; (Jones-Gotman & Milner, 1977)). The results indicate that, overall, glucose enhanced performance on the 20-minute recall of the Complex Figure Test (Rey and Taylor) as well as on the verbal and figural fluency. Peak glycemic increases inversely predicted dichotic listening performance and verbal fluency. The findings of this study suggest that in older nondiabetic adults, poorer glucose regulation also appears to be associated with reduced auditory attention and executive function. In addition, although glucose ingestion appears to improve performance on nonverbal memory and overall fluency, the pattern of correlations suggests that glucose may attenuate some performance decrements observed in worse glucose regulators.

More recently, Riby, Meikle, and Glover (2004) conducted a within-subjects crossover design in which the performance of 20 older adults (mean age = 69 years) was evaluated following both, glucose and saccharin ingestion (one week apart). The tests employed in this study included measures of immediate and delayed episodic memory (single task: encoding paired-associates and dual task: encoding paired-associates while sorting cards); Digit symbol substitution (processing speed; WAIS-III; (Wechsler, 1987); mental control (mental manipulation; WMS-III; (Wechsler, 1987); Digit Span (Forward and Backword; working memory, WMS-III; (Wechsler, 1987); and category fluency. The findings revealed that glucose facilitated the immediate recall of the word list (paired associates), with no effects on the other measures. Furthermore, higher change in glucose levels (compared to fasting) in both the glucose and saccharin conditions were significantly correlated with immediate and delayed recalls (single and dual tasks) as well as with digit symbol substitution and digit span backwards in the glucose condition.

The results of the studies described above reflect that in older nondiabetic adults, worse glucose regulation is primarily associated with decrements in verbal and nonverbal memory, executive function, and auditory attention. The findings also reflect that when a comprehensive evaluation of overall cognitive function is conducted, verbal declarative memory tasks appear to be most sensitive to glucoregulatory effects. Furthermore, the effects of glucose administration appear to interact with glucose regulation: glucose appears to improve most of the performance decrements observed in worse glucose regulators.

To directly evaluate the interactive effect of glucose ingestion on the performance of better or worse glucose regulators, other investigators measured the performance of 27

young (mean age = 21 years) and 32 older adults (mean age = 69 years) using a repeated-measures counterbalanced design across multiple cognitive functions (S. Craft, Murphy, & Wemstrom, 1994). The tests included: paragraph recall (immediate and 10-minute delayed recall), a modified version of the California Verbal Learning Test (immediate and 15-minute delayed recall and recognition; (Delis, Kramer, Kaplan, & Ober, 1987; Delis, McKee, Massman, Kramer, & Kaplan, 1991), pattern recognition and recall (3 checkboard patterns), serial reaction time (implicit motor memory; (Nissen, Willingham, & Hartman, 1989), Paced Serial Addition Test (working memory task involving addition;(Gronwall & Sampson, 1974), verbal fluency (Benton, 1968), and Stroop color-word interference test (Stroop, 1935). Furthermore, in addition to evaluating the interactive effects of glucose ingestion, gender effects were also evaluated to further investigate the factors contributing to the differential performance of better and worse regulators. Glucose regulation was estimated using a recovery index in which fasting glucose levels were subtracted from 60-minute glucose levels obtained in the glucose condition. Median splits using the recovery indices were utilized to divide the participants into better and worse glucose regulators.

Comparisons of the performance scores between the saccharin and glucose conditions (difference scores) revealed that older males who showed better glucose regulation were superior in their performance following glucose ingestion on the immediate and delayed paragraph recalls compared to older males who showed worse glucose regulation. On the pattern recall task, however, older males who showed worse glucose regulation appeared to perform better in comparison to the older males who showed better glucose regulation independent of glucose solution. Furthermore, glucose

appeared to differentially affect the performance of the young males only: the performance of males who showed worse glucose regulation improved under the glucose condition whereas the performance of males who showed better glucose regulation worsened under the glucose condition.

In summary, this study further substantiates the suggestion that impaired glucose regulation is associated with decrements in memory and as demonstrated by Hall et al., (1989), and Manning et al. (1990), glucose ingestion appears to reverse the decrements of worse regulators. Furthermore, there appears to be a detrimental effect of glucose on cognitive performance in individuals who regulate glucose more effectively. In addition, this study suggests that glucoregulatory effects on cognitive performance appear to be more observable in males. Alternatively, it is also possible that the detrimental effects of glucose on the performance of better regulators and the observed gender effects reflect sample variability and the possibility of type 2 error observed in relatively small samples.

Another recent study also directly evaluated the interacting effects of glucose and gender on the performance of 15 older adults (mean age = 62 years) using the following tests of the WMS-R (Wechsler, 1987): Logical memory (immediate and delayed recall), Digit Span, Visual Memory Span, and Verbal Paired Associates (Messier, Gagnon, & Knott, 1997). Participants also received the Digit Symbol Test (WAIS-R; (Wechsler, 1981), the Cancellation H Test (M. Lezak, 1983) and the cognitive portion of the Alzheimer's Disease Assessment Scale (Rosen, Mohs, & Davis, 1984). Again, each participant served as his or her own control and was evaluated under both glucose and saccharin conditions. Furthermore, a recovery index, similar to the index obtained by Craft et al., (1994) was computed by subtracting 75-minute glucose levels from baseline

glucose levels obtained in the glucose condition and median splits using this index were also utilized to divide the sample into better and worse glucose regulators. The findings of this study demonstrated that males identified as poor regulators performed worse on the immediate and delayed recall of the Logical Memory test, the Digit Span Backwards as well as on the word recognition subtest and on the recall subtest of the ADAS (10-word list presented 3 times). Glucose appeared to attenuate some performance decrements, as observed on the word recall subset of the ADAS and on the Digit Span Backwards. The findings also revealed that females identified as poor regulators performed worse on the Digit Span Forwards and as observed in males, glucose appeared to attenuate the performance decrements of these females. On the other hand, glucose appeared to impede the performance of females who showed better glucose regulation.

Overall, the findings of this study further substantiate previous observations in that verbal memory and auditory attention appear to be associated with glucose regulation and that the administration of glucose appears to attenuate the decrements observed in poor regulators. Furthermore, this study also demonstrates that glucose regulation appears to have a differential effect on the performance of males and females, with the performance of males being more affected by impaired glucose regulation, a finding previously observed by Craft et al., (1994). Finally, the findings also suggest that glucose may have a differential effect on the performance of better and worse glucose regulators. In evaluating the glucoregulatory status of the samples assessed in the two studies that demonstrated interactions between glucose and glucose regulation (S. Craft, Murphy, & Wemstrom, 1994; Messier, Gagnon, & Knott, 1997), glucose appears to impede the

performance of the groups showing the best glucoregulation in comparison to the other groups assessed.

More recently, the interacting effects of glucoregulation and glucose ingestion on verbal memory of males and females was also evaluated in young adults (mean age: 21.3 years; (Messier, Desrochers, & Gagnon, 1999). Verbal memory was assessed using word-recall measures following presentations of high- and low-imagery word lists. Initially, participants were presented with one practice list of 10 words. This was followed by 4 experimental lists of 20 words each presented at a rate of one word per second. Recall was obtained immediately following the presentation of each list (immediate recall) and 15 minutes following the last list presentation of all lists (delayed recall). A repeated-measures design was also employed in which each participant was tested twice: once under the glucose condition and once under the saccharin condition with order of solution counterbalanced across the two visits. Glucose regulation was defined using median splits of the recovery indices calculated for each gender. Recovery indices were defined as the difference between 60-minute evoked glucose levels and fasting glucose levels obtained from the glucose condition.

The findings of this study demonstrated that participants classified as poor regulators recalled less words at both the immediate and delayed recalls compared to those classified as good regulators. Furthermore, as observed in the previous studies of comparable methodology (S. Craft, Murphy, & Wemstrom, 1994; Messier, Gagnon, & Knott, 1997), glucose appeared to reverse the performance decrements observed in the poor regulators. Contrary to the findings observed in the Craft et al., (1994) and the

Messier et al., (1997) studies, Messier et al., (1999), however, found no gender differences in performance associated with glucoregulatory effects.

Another more recent study evaluating glucose regulation and cognitive performance in younger adults used several glucoregulatory indices to determine the indices most associated with cognitive performance (R T Donohoe & Benton, 2000). The sample consisted of 46 females (mean age = 22 years). Testing was conducted over two sessions, separated by 1 week: For the first session, glucose regulation was determined using indices derived from a glucose tolerance test, in which blood samples were collected at half hourly intervals for a total of 3.5 hours following the ingestion of a 50g glucose solution. The following indices were obtained: fasting blood glucose levels; area under the curve of glucose; time to baseline (time of glucose recovery back to baseline values; area below baseline (after glucose levels fell below baseline to baseline); rate of rise from baseline to peak; time to peak; peak; nadir (lowest glucose value); rate of fall from peak to nadir; time to nadir. For the following testing session, dietary restrictions were not enforced nor was the ingestion of any solution and all subjects had, by choice, consumed breakfast. Participants were assessed on three cognitive measures. The first measure was a verbal memory measure, which involved the immediate and 15-minute delayed recall of 30 nouns presented using an auditory modality. The second measure was a reaction time measure in which participants were required to press buttons in response to illuminating lights. This task was performed on four occasions, during which one, two, four, or eight lamps could illuminate. The final measure was an attentional task in which participants were required to detect sequences of three consecutive odd or even digits presented visually for a period of 5 minutes.

The findings of this study demonstrated that higher peak glucose values following glucose ingestion were inversely related to performance on the attentional task. The authors also observed that the time between the lowest glucose level and its return to baseline was related to the immediate and delayed recalls of the word list. This last index, however, was only obtained from 31 participants because many participants' glucose did not return to baseline over the 3.5 hour-period. Finally, following an evaluation of blood glucose levels during the cognitive testing, it was reported that higher baseline glucose was associated with faster decision times when monitoring eight lamps and overall less intra-individual variability in decision times on the reaction time measure. In summary, although some of the findings are difficult to interpret, there is some suggestion that individuals who show worse regulation, as defined by higher evoked glucose (peak) or by faster glucose upregulation to baseline, show decrements in cognitive performance compared to those who appear to regulate glucose more efficiently.

Other glucoregulatory indices as well as the influence of glucose and common carbohydrate foods were evaluated in another recent study on cognitive function in older adults with normal glucose regulation (R J Kaplan, Greenwood, Winocur, & Wolever, 2000). In this study, twenty participants were recruited (mean age: 72 years) and were tested under the four conditions of the repeated-measures crossover design. The conditions included glucose, instant mashed potatoes, barley or placebo, which were administered following an overnight 10-12-hour fast. Participants were blinded to the placebo and glucose conditions. Each treatment contained 50 g. of carbohydrates, however, given that mashed potatoes have a high glycemic index and that barley has a

low glycemic index, the effects of blood glucose levels independent of carbohydrate effects were evaluated. Glucose levels were obtained at fasting and at 15, 60 and 105 minutes following ingestion. All participants were tested on the following measures, in the same order, 15-minutes and 60 minutes after consumption: a variation of the Rey Auditory-Verbal Learning Test (immediate and 20-minute delay recall of 12 words; (Spreen & Strauss, 1998); recall of an audiotaped narrative paragraph (Morris, Kunka, & Rossini, 1997; Wechsler, 1987, 1997b); Trails B (executive/visuomotor; (Reitan & Wolfson, 1985); and an attention task requiring participants to attend to specific aspects of a television program. At 105 minutes, participants were given the immediate word list recall and trails B only.

There were four glucoregulatory indices evaluated: incremental area under the glucose curve across all sampling; estimated β cell function using the homeostasis model of assessment (HOMA; (D. R. Matthews et al., 1985); estimated insulin resistance using HOMA; and body mass index. The HOMA model uses fasting insulin and glucose levels to produce an estimate of beta cell function (expressed as a percentage of the estimate for 35-year old (or less) normal-weight subjects) and insulin resistance. The results of this study demonstrated that higher incremental area under the glucose curve appeared to be associated with poorer paragraph recall, word list recall (first presentation), and Trails B performance, although only the latter two were statistically significant. Higher insulin resistance was associated with superior paragraph recall (delayed) and a trend was observed for immediate paragraph recall and Trails B performance. Body mass index was also observed to be positively associated with paragraph recall, and word list recall (first presentation). The multiple regression analyses demonstrated that the indices

accounted for between 38-47% of the variation in paragraph recall, word list recall (first presentation), and Trails performance. The authors indicated that although there was no significant linear associations with poor (low) β cell function, the multiple regression analyses demonstrated that β cell function was a significant predictor of cognitive performance. These findings suggest that high evoked glucose, poor β cell function, good insulin sensitivity, and low BMI were associated with poorer performance on verbal memory and executive tasks but not on visual/auditory attention tasks.

No differences in cognitive performance were observed after consumption of glucose, potatoes, or barley compared to placebo. However, when measures of baseline performance and glucose regulation were factored in, poor β cell function was associated with improved paragraph recall for all 3 carbohydrates and poorer baseline paragraph recall was associated with enhanced performance after potato and barley ingestion. Furthermore, the authors also reported that subjects with good baseline memory performance actually performed worse when they consumed carbohydrates. Although similar trends were observed for the word list recall, high fasting glucose levels were significantly associated with improvements with ingestion of glucose and barley. When evaluating Trails B performance, a similar pattern of results was observed to the paragraph recall findings: poor β cell function and baseline performance, high gAUC, and good insulin sensitivity were associated with improvement in performance. The authors also observed that although no gender differences were observed on the verbal memory measures, the associations were stronger for women's performance on the Trails B compared to men's performance. Furthermore, men with poor baseline attention and all women performed better with barley than with placebo on the attention task.

Overall, some findings of this study substantiate previous observations that impaired glucose regulation is associated with impaired cognitive performance, in particular, verbal memory and executive function. In addition, this study was the first to report that carbohydrates can reverse performance decrements, independent of actual glucose levels. On the other hand, as observed in Craft et al.,'s (1994) and Messier et al.,'s, (1997) studies, carbohydrates can also impede performance for those with better glucose regulation or better baseline performance. Furthermore, the authors indicated that although some gender differences were reported, the findings were not systematic.

More recently, a population study was conducted to evaluate the relationship between insulin resistance and cognitive function in older healthy adults. Abbatecola et al. (2004) evaluated the performance of 578 older adults (273 males; mean age = 73 years) and 218 middle-aged adults (103 males; mean age = 43 years) on measures of the Trail Making Test (TMT; Part A, Part B, Difference between A and B) (M. D. Lezak, 1995). They also used the homeostasis model assessment (HOMA) to estimate degree of insulin resistance and divided the sample according to the HOMA tertiles. They found that older adults in the 3rd HOMA tertile (worse insulin resistance) had longer TMT-Part B and Difference scores compared to the older adults in the first and second tertiles. Similarly, subjects in the middle tertile showed longer TMT-Part A and TMT-Part B scores. HOMA insulin resistance index was significantly associated with all measures of the TMT in the older and middle-aged groups even following adjustments for age, sex, education, high-density lipoprotein cholesterol, triglycerides, total insulin-like growth factor, hypertension, drug intake, physical activity, body mass index, waist-hip ratio, depression, history of stroke, and MMSE performance.

Another large study evaluated glucose regulation in 111 healthy older men (mean age = 68 years) using glycosylated hemoglobin ($HbA1_c$) (MacLullich, Deary, Starr, Walker, & Secki, 2004). They correlated $HbA1_c$ with performance on measures of verbal memory (word-list learning, Rey Auditory-Verbal Memory Test (RAVMT), immediate and 24-hour delayed paragraph recall-WMS-III, 1997), visuospatial memory (Visual Reproduction-WMS-III, 1997; Benton Visual Retention Test), verbal fluency, fluid intelligence (Raven's Standard Progressive Matrices), processing speed (Digit-Symbol Substitution Test), and an estimate of premorbid intelligence (National Adult Reading Test). The findings were consistent with previous observations and revealed that worse regulation (i.e., higher levels of $HbA1_c$) was associated with poorer performance on two verbal memory measures, the RAVLT and delayed paragraph recall.

In summary, the findings of studies evaluating glucoregulatory effects in nondiabetic adults suggest that older and younger individuals classified as having impaired or relatively worse glucose regulation show decrements in overall cognitive performance. These findings also suggest that glucose regulation is a marker of mild cognitive decrements, accounting for almost half of the variation in performance differences, independent of glucose levels. This conclusion is also supported by the observation that neuroelectrophysiologic activity appears to differentiate better and worse glucose regulators during euglycemia (Knott, Messier, Mahoney, & Gagnon, 2001). The ingestion of carbohydrate, protein, and fat may attenuate the reduction in glucose utilization and reverse some of the decrements whilst impeding the performance of those who show relatively better glucose regulation. The findings evaluating the interactive effects of gender are not entirely consistent: some studies have shown that males are

more sensitive to glucoregulatory effects (S. Craft, Murphy, & Wemstrom, 1994; Messier, Gagnon, & Knott, 1997), while others have shown no differences between the genders (Messier, Desrochers, & Gagnon, 1999; Vanhanen et al., 1997). Although intra-group variability in glucose regulation might account for the inconsistent findings, additional studies are needed to substantiate gender effects.

The following sections provide an overview of the underlying mechanisms that have been proposed to account for the observed individual changes in cognitive performance following carbohydrate and overall energy intake. Prior to the following discussions, it is important to determine whether the decrements associated with poor glucoregulation and hyperglycemic facilitation are the result of a global cognitive effect in which general attention is improved, or whether the facilitation is specific to a memory process. One study evaluated the story recall of participants in conditions where glucose was administered either before or following story acquisition (C. A. Manning, Parsons, & Gold, 1992). Manning et al., (1992) reported that glucose improved recall at both time intervals, suggesting that the facilitative effect of glucose involves a memory process. In another study, story recall of participants ingesting glucose shortly before acquisition of the story was compared to story recall of those ingesting glucose shortly before the recall (C. A. Manning, Stone, Korol, & Gold, 1998). Although hyperglycemic facilitation was observed in both cases, performance was superior when glucose was administered before the acquisition phase rather than the recall phase of the test. Thus, although it is possible that glucose acts on different cognitive processes involved in learning, including attention, working memory, executive functions, encoding, and retrieval, the results of

these two studies suggest that the hyperglycemic facilitation involves memory encoding, which can be observed in the absence of transient blood glucose elevations.

Peripheral Mechanisms of Action Involved in Glucose-Mediated Cognitive Enhancement

Recent reports of cognitive enhancement following carbohydrates, protein and fat suggest that the cognitive enhancement does not appear to be specific to central glucose-mediated effects (R. J. Kaplan, Greenwood, Winocur, & Wolever, 2001). In addition, one study demonstrated that glucose and fructose both appear to affect recently acquired memories with comparable cubic dose-response functions in rats (Rodriguez, Horne, Mondragon, & Phelps, 1994). Rodriguez et al., (1994) suggested that because fructose does not readily pass the blood-brain barrier, the mechanism of action of the two monosaccharides might involve peripheral pathways.

One mechanism of action that has been proposed to account for both glucose and fructose effects and could account for the effects of other nutrients (i.e., fat and protein) involves neural signals carried via the vagus nerve to the brain (Messier & White, 1987). Messier and White (1997) described that changes in cell membrane transport in the liver following high doses of glucose or fructose that are transduced into neural signals and travel via the celiac ganglion and the vagus nerve to the brain could act on cognitive function. This hypothesis was based on the observation that lesions to the celiac ganglion have been shown to abolish the effects of glucose on memory (White, 1991). More recently, this view has been supported by data suggesting that vagotomy appears to block the memory-enhancing effects of peripherally-injected drugs (Flood, Mooradian, & Morley, 1990) and that stimulation of the vagus nerve in human participants enhanced retention on a word-recognition memory task (Clark, Naritoku, Smith, Browning, &

Jensen, 1999). Clark et al., described several mechanisms that could account for the cognitive effects of vagus stimulation. One mechanism involves the vagus nerve's role in the mediation cardiopulmonary reflexes and complex visceroendocrine responses that modulate memory storage. Another mechanism involves the transmission of vagal signals: Memory is enhanced by vagal stimulation intensities that likely involve myelinated axons transmitting mechanoreceptor signals from thoracic organs to the brain. Clark et al., also suggested that the cognitive effects mediated by vagus nerve stimulation could be mediated by electrophysiological and metabolic changes in the forebrain and brainstem structures involved in memory.

Although glucose readily passes the blood brain barrier, several studies have demonstrated that cognitive enhancement following glucose ingestion could also involve a peripheral function of glucose (Boccia, Kopf, & Baratti, 1999; J. L. Hall, Reilly, Cottrill, Stone, & Gold, 1992). These studies demonstrated that phlorizin, a substance that has a high affinity for the extracellular portion of the glucose transporter, enhanced memory. Given that phlorizin did not have an effect on blood glucose regulation and brain glucose uptake, one possible mechanism of memory enhancement appears to be related to intracellular signaling triggered by binding.

Central Mechanisms of Action Involved in Glucose-Mediated Cognitive Enhancement

Using microinjections or infusions of glucose directly in the central nervous system, it has been demonstrated that glucose appears to act directly on brain function to produce its effects on memory (Lee, Graham, & Gold, 1988). One hypothesis for this effect is that glucose improves memory because of the increased availability of glucose to the brain. However, as discussed by Messier (2004), this hypothesis is weakened by the

findings that only a limited number of glucose doses appear to improve memory despite different doses of glucose resulting in equivalent blood glucose levels (Messier, 2004; Messier, Pierre, Desrochers, & Gravel, 1998; Messier & White, 1987). Another hypothesis is that locally, glucose supply may not be optimal under conditions of increased neuronal activity and that peripheral glucose increases may selectively raise extracellular brain glucose levels in these regions. In support of this view are findings that have shown that hippocampal neuronal activation produced by training on a memory task result extracellular glucose level decreases in the hippocampus (E. C. McNay, Fries, & Gold, 2000), which appear to be alleviated by peripheral glucose administration that also led to improvement in memory performance. However, this hypothesis does not account for the finding that only limited doses of glucose are effective.

It has also been proposed that the memory enhancing effects of glucose could involve interactions with forebrain cholinergic systems by increasing the synthesis of acetylcoenzyme A (used to synthesis acetylcholine), which is derived from glucose metabolism (Messier, 2004; Messier & Gagnon, 2000). This hypothesis is supported by several studies demonstrating a relationship between glucose activity and activation of the hippocampal cholinergic system associated with memory enhancement (Messier & Destrade, 1994; Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Ragozzino, Unick, & Gold, 1996). The interaction between glucose regulation and cholinergic systems has also been observed in studies of experimental diabetes, which demonstrated that experimental diabetes reduces the availability of acetylcholine in synapses(Lakhman & Kaur, 1994). The relationship between glucose and cholinergic function was also observed in studies evaluating interactions of glucose and scopolamine, a central

cholinergic antagonist (Durkin, Messier, de Boer, & Westerink, 1992; Messier, 1998). Durkin et al., (1992) demonstrated that scopolamine resulted in a 1200% increase in acetylcholine release while glucose further increased acetylcholine release to 1700% of baseline. Studies evaluating behaviour-driven neuronal activation, however, have shown only a 36 - 50% increase in acetylcholine release from baseline (Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Ragozzino, Unick, & Gold, 1996), suggesting that the behaviour-driven neuronal activation does not appear to deplete acetylcholine stores given that glucose can induce a release up to 1700% of baseline. Thus, the facilitative effect of glucose does not appear to be mediated by the increases in acetylcholine synthesis (Messier, 2004). Furthermore, the observation that certain glucose doses (higher doses) neither improve memory nor increase acetylcholine release (Ragozzino, Unick, & Gold, 1996) and that a suboptimal glucose dose combined with a suboptimal choline dose (unlikely elevated blood or brain glucose) can facilitate memory (Kopf, Buchholzer, Hilgert, Loffelholz, & Klein, 2001) argue against the hypothesis that the memory enhancing effects of glucose are caused by acytelcholine synthesis.

Given that insulin is secreted in response to increasing concentrations of glucose in the blood, insulin-mediated effects have also been proposed as another central mechanism of action to account for the memory-enhancement effects of glucose. Until recently, it was believed that insulin's action was limited to the periphery. It is now known that insulin crosses the blood-brain barrier (Banks, Jaspan, & Kastin, 1997) and that insulin receptors are observed in the olfactory bulb, hypothalamus, hippocampal areas CA1 and CA3, dentate gyrus, cerebral cortex, cerebellum, and choroid plexus (Folli, Ghidella, Bonfanti, Kahn, & Merighi, 1996; Hill, Lesniak, Pert, & Roth, 1986;

Schwartz, Figlewicz, Baskin, Woods, & Porte, 1992; Unger, Livingston, & Moss, 1991; Werther et al., 1987). Serum insulin concentration has been shown to be associated with concentrations of insulin in the cerebrospinal fluid (Baura et al., 1993) and induced hyperinsulinemia has been shown to be associated with increased insulin binding in the CA1 region of the hippocampus (Marfaing et al., 1990) suggesting a relationship between peripheral and central insulin activity.

The recent discovery of the insulin-sensitive glucose transporter GLUT-4 and GLUT-8 in various brain regions including the hippocampus (El Messari et al., 1998; Leloup et al., 1996; McCall et al., 1997; McEwen & Reagan, 2004) suggests that cognitive function could be affected by insulin-dependent glucose transport (Park, 2001). Insulin receptors have also been identified on post-synaptic neurons in the brain, which suggests that insulin could have cognitive effects through its role in ion transport and intracellular ion concentrations (Park, 2001).

Another mechanism of action of insulin on cognitive function could result from its interaction with other hormones such as peptide cholecystokinin, which has independently been shown to affect memory (Crawley & Corwin, 1994). Furthermore, insulin-like growth factor-I (IGF-I), a member of the insulin family, sharing structural and functional characteristics, has been found to have a neuroprotective role in Alzheimer's disease (Connor et al., 1997) and has been shown to be directly related to cognitive performance of older adults (Aleman et al., 1999; Rollero et al., 1998). The direct effects of insulin on cognition have also been shown in studies evaluating the effects of intranasal insulin administration. These studies have demonstrated EEG changes (Kern, Born, Schreiber, & Fehm, 1999) and positive cognitive effects, including

improved memory in healthy participants (Benedict et al., 2004) and in Alzheimer's disease patients (Baker et al., 2003; Reger MA et al., 2006) following repeated intranasal insulin administration.

In summary, there appears to be several mechanisms of action involved in the observed cognitive enhancement following energy intake. Although these mechanisms could involve initial peripheral action (e.g., stimulation of the vagus nerve), they appear to independently affect central function to improve cognitive performance. Furthermore, the effects of glucose and insulin on cognitive function appear to be mediated by peripheral or central actions or both.

Objectives and Hypotheses for the Study

The primary purpose of this study was to conduct a comprehensive evaluation of cognitive functions to determine the relative sensitivity of verbal memory to glucose regulation and whether other cognitive functions are also susceptible to poor glucose control. Previous studies to date have generally been limited in their power to determine significant associations and have thus been susceptible to type 2 error. Indeed, all studies evaluating the effects of glucose regulation in a young sample have employed relatively small samples, and/or have used relatively limited cognitive batteries, that have either lacked in the number of neuropsychological functions evaluated or in the standardization of the assessments (see Appendix B). Given that the effects of glucose regulation on cognitive function are likely to be small because of the lack of pathology in a young nondiabetic sample and the large variability in normal neuropsychological test performance, a large sample would be needed to determine whether the documented glucoregulatory effects to date are indeed true effects.

Although, a pure experimental design was not possible given that poor glucose regulation was not induced in participants, an attempt was made to determine the relationship between the various cognitive functions and glucose regulation. Past research has demonstrated that type 2 diabetes patients and participants with impaired glucose tolerance show decrements in global cognitive screening measures and more specifically, in verbal memory. In addition, nondiabetes patients with poorer glucose regulation also show decrements in verbal memory as well as in processing speed and executive function. Given that verbal memory appears to be the most consistent decrement observed across various glucoregulatory groups, it was hypothesized that poorer glucose regulation would be associated with poorer performance on measures of verbal memory. It is not clear to date, the relationship between other measures of cognitive function and glucose regulation, therefore, exploratory analyses using multiple validated neuropsychological measures were conducted to determine the specific cognitive functions associated with glucose regulation and to substantiate previous observations using a large sample size.

A second important objective of the study was to determine the most reliable biological marker of cognitive decrements associated with impaired glucoregulation in a large sample of young nondiabetic adults (e.g., estimates of beta-cell function and insulin resistance). Several glucose indices have been previously evaluated in studies of nondiabetic adults, however the relative sensitivity of these indices to cognitive decrements is unclear. Identifying a valid and reliable biological marker of cognitive decrements in a large sample could facilitate future investigations in employing appropriate methodology and in targeting cognitive decrements as well as offer some

insight to the underlying mechanisms associated with the observed variability in cognitive function. In nondiabetic adults, it has been shown that evoked measures of glucose appear to be the most sensitive predictors of cognitive decrements. It was, therefore, hypothesized that indices reflecting evoked glucose levels will likely be most related to cognitive function.

Another important objective of this study was to determine the potential contribution of vascular risk factors to cognitive function in a young nondiabetic sample, which, to date, has not yet been evaluated. These factors include total triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels as well as body mass index, and exercise. Vascular disorders are associated with hyperinsulinemia and type 2 diabetes, the extreme form of impaired glucose regulation, and likely interact with type 2 diabetes cognitive performance. In addition, they have been independently associated with cognitive decrements. Although, it was predicted that vascular risk factors would unlikely contribute significantly to the cognitive variability in a young nondiabetic population, it was important to rule out the potential of vascular contributors.

As indicated above, it is not clear from previous studies whether gender interacts with the performance of participants with varying levels of glucose regulation (better, average, worse regulation). The findings of studies evaluating nondiabetes patients as well as participants with impaired glucose tolerance and diabetes patients are inconsistent. Thus, another objective of this study was to determine the relative contribution of gender effects, if any, using a larger sample size and a more comprehensive cognitive evaluation than what has previously been conducted.

Finally, another goal of the present study, was to evaluate the effects of glucose ingestion on cognitive function of participants identified as better, average or worse glucose regulators using a double-blind mixed-repeated measures design in which each participant was tested twice (following glucose ingestion and following saccharin ingestion) to determine hyperglycemic effects while statistically controlling for practice or order effects. Given that hyperglycemic effects were evaluated using a repeated-measures design, it was more likely to observe differences that can be attributed to the effects of solution than to between-subjects variables or group differences. Findings to date appear to suggest that glucose will likely reverse the performance decrements of nondiabetic worse regulators, therefore, similar observations were predicted using the larger sample of nondiabetic adults.

Method

The research protocol of this proposal has been approved by the Ethics Committee of the University of Ottawa.

Participants

Recruitment. Participants for this study were recruited from undergraduate courses offered at the University of Ottawa. Although sampling was not randomized from the entire population of young adults, participants were relatively comparable in their level of education and socioeconomic status. A short rationale and description of the study (approximately 5 minutes in length) was presented to the students in which they were informed of the relationship observed between glucose regulation and cognitive function as well as the procedure involved in the first, second and third sessions of the study (see Appendix C for Recruitment Script). The students were also informed that

their participation is voluntary and confidential and is independent of their course and program requirements.

Following the presentation, any potential questions that the students had regarding the details of the study were addressed and interested students had the opportunity to indicate their names and phone numbers on circulating "sign-up" sheets. Interested students were informed that they would be contacted to further discuss the study and to determine whether they meet established criteria for the study.

Screening. Following the class presentation, all interested students were contacted in order to determine whether they meet established health criteria for the study and to potentially schedule the first session of the study (see Appendix D for Telephone Health Screening Interview). They were informed that their answers would be strictly confidential and that in the event that they are not included in the study, their answers would be immediately destroyed.

Initially, the students' ages and gender were obtained. The interview then addressed several factors that may potentially confound glucoregulatory indices as well as cognitive performance. More specifically, students reporting being treated for diabetes, or having a history of hypoglycemia, neurological disorders or lesions including cerebral hemorrhages, tumors, strokes, or head injuries with loss of consciousness were not included in the study. Students were also screened for alcohol and drug abuse in the precedent year. The consumption of more than 54g of ethanol per day (the equivalent of 4 drinks) for a period exceeding 1 month as assessed through a semi-structured interview used to measure alcoholic consumption history variables (Skinner, 1982; Skinner &

Allen, 1982) resulted in exclusion. The daily use of marijuana as well as history of other illicit or psychoactive drug use also resulted in exclusion.

Furthermore, given the association between decrements in cognitive function and depression (Gallassi, Morreale, & Pagni, 2001), students reporting depressive symptomatology associated with the Diagnostic and Statistical Manual of Mental Disorder, 4th edition (American Psychiatric Association, 1994) criteria for Major Depressive Episode were not included in the study. More specifically, students indicating generally feeling sad, feeling tearful, and a general loss of interest or pleasure were excluded. Although this procedure may not have been the most reliable in assessing depressive symptomatology, the purpose was merely to obtain a general screening for depressive symptomatology. In addition, depressive symptomatology was further assessed with the Beck Depression Inventory (Beck, 1987) administered at the first session of the study. The BDI was selected because of its simplicity of administration, scoring and interpretation as well as its associated validity and reliability. Only participants whose scores fell within the minimal or mild ranges (Beck, 1987) were included in the study to further screen out participants with depressive symptoms.

During the interview process, in the event that a student met an exclusion criterion, he or she was immediately informed of this and the interview sheet was destroyed. On the other hand, when a student met the criteria for the study, the first session was then scheduled. The student was informed that he or she would have to fast from midnight before the first session and that fasting is defined as not eating or drinking anything except for water. This fasting protocol follows protocols that have been previously used in glucoregulatory studies (S. Craft, Murphy, & Wemstrom, 1994;

Messier, Desrochers, & Gagnon, 1999). In addition, one study demonstrated hyperglycemic facilitation following an overnight fast or a 2-hour fast following breakfast or lunch suggesting that the specific fasting duration does appear to play a role in observed hyperglycemic facilitation (Sunram-Lea, Foster, Durlach, & Perez, 2001). At the end of the interview, the student was informed that he or she would be contacted one day prior to each session to reconfirm the appointment.

Biological Measures

All blood sample tests were conducted by DynaCare laboratories, which normally processes all tests conducted at the University of Ottawa Health Centre. Blood samples were obtained from venous punctures by a nurse. More specifically, a fasting blood sample was obtained to determine fasting glucose levels (Glucose oxidase-Roche Modular Glucose method using Vitros 750 XRC Series apparatus), 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. Cholesterol and triglyceride levels were obtained because of their association with impaired glucose regulation and cognitive function (Desmond, Tatemichi, Paik, & Stern, 1993; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992; Kilander, Nyman, Boberg, & Lithell, 1997; Vanhanen et al., 1998; Vanhanen et al., 1999) to determine the potential interactive effects of cardiovascular risk factors. The fasting blood sample was

also utilized to obtain fasting insulin levels, however, some samples were measured using Chemiluminescent Immunoassay using DPC-Immunlite or Roche Elecsys 2010 and others, using a radioimmunoassay method using DPC Coat-A-Count. Similarly for the evaluation of c-peptide levels, which were also of interest given the relationship between c-peptide levels and beta-cell function of the pancreas, some samples were measured using Chemiluminescent Immunoassay using DPC-Immunlite and others, using a radioimmunoassay method using EURO/DPC's Double Antibody C-Peptide. The two differing methods of analyses for insulin and c-peptide levels was the result of experimenter error: Dynacare laboratories changed their methodology for insulin and c-peptide analyses during the data collection period without the experimenter's knowledge and thus, approximately half the participants' samples were analyzed using chemiluminescent immunoassay and the other half, using radioimmunoassay. Although the two methods are not expected to yield clinically significant differences, significant differences were observed between the two techniques and are discussed in light of the present findings (see Results and Discussion).

Following the collection of the fasting blood sample, participants were then administered the oral glucose tolerance test (OGTT). A 75g glucose solution (296 ml.) was ingested and blood samples were obtained to measure glucose at fasting, 30, 60 and 120 minutes post-ingestion and insulin at fasting, 60 and 120 minutes post-ingestion. The OGTT was originally developed to estimate carbohydrate tolerance. However, given that glucose and insulin responses reflect pancreatic B-cell secretion of insulin and the sensitivity of tissue to insulin, the OGTT has also been used to estimate B-cell function and insulin action (Stumvoll M et al., 2000). It is to be noted that the "gold standard" for

assessing B-cell function and insulin sensitivity are the hyperglycemic and euglycemic-hyperinsulinemic clamps (DeFronzo RA, Tobin JD, & R., 1979; DeFronzo, Tobin, & Andres, 1979) during which blood glucose is either clamped at hyperglycemic levels (~20mmol/L) or at euglycemic levels (~5.6 mmol/L) by infusing insulin and/or glucose. Samples of plasma insulin and glucose are obtained throughout the clamping technique to monitor glucose levels and insulin secretion. Although most reliable, this technique is very costly and requires significant resources and time, which were not available for the present study. Therefore, estimates of carbohydrate tolerance, including insulin action were obtained using glucose and insulin indices derived from the OGTT.

In evaluating the reliability of the glucose tolerance test, one study tested 889 adult males and found that the mean difference in glucose values between a first and second glucose tolerance test was < -1% at fasting and –15% 2 hours post-ingestion (Eriksson & Lindgarde, 1990). Eriksson and Lindgarde (1990) observed that 62% of those with initially impaired glucose tolerance had normalized by the repeat test. It is important to note that the glucose regulation measures in the present study were not used to determine whether each participant met an established glucoregulatory criteria, instead, glucose regulation measures will be used to compare participants' glucoregulatory status to the status of others in the sample. Given that the comparison is within the sample, measurement error should be comparable for all participants.

Based on the findings of an initial study conducted in our laboratory (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002), university students' glucose values in response to the glucose tolerance test typically peak at 30 minutes and decline to baseline/fasting levels at 2 hours. The rate of decline appears to be more rapid between

30 and 60 minutes than between 60 and 120 minutes. The glucoregulatory indices that were evaluated for their relationship with cognitive performance in this study include glucose recovery indices that have been previously used (Abbatecola et al., 2004; Azari, 1991; S. Craft, Murphy, & Wemstrom, 1994; R T Donohoe & Benton, 2000; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997; Vanhanen et al., 1998), which appear to reflect insulin sensitivity (Stumvoll M et al., 2000). These were evaluated in the present analyses to allow for comparisons with previous findings. In addition, other OGTT-derived measures that have shown significant correlations with the metabolic clearance rate of glucose (average glucose infusion rate during the last hour of the euglycemic clamp divided by the average glucose concentration) as well as insulin sensitivity (average glucose infusion rate divided by the average glucose concentration during the same interval) in a nondiabetic sample (Stumvoll M et al., 2000) (see Table 1 for operational definitions of all indices) were also evaluated. These included fasting and 2-hour insulin levels as well as glucose levels. Finally, two other OGTT-derived indices of insulin sensitivity that have shown strong correlations with the hyperinsulinemic euglycemic glucose clamp were also investigated: QUICKI (Abbatecola et al., 2004; Katz A et al., 2000) and ISICOMP (Matsuda M. & DeFronzo R.A., 1999). QUICKI has shown superior correlations with the hyperinsulinemic euglycemic glucose clamp compared to the minimal model analysis in nonobese, obese and type 2 diabetes subjects, to the homeostasis model assessment of insulin resistance index (HOMA-IR) and to insulin measures from the hyperglycemic clamp in children

Table 1
Glucoregulatory Indices (Glucose Tolerance Test) that were Evaluated.

Index	Definition
Insulin Sensitivity/Metabolic Clearance Rate	
Fasting Glucose	Glucose level at fasting (mmol/L)
30-Minute Glucose	Glucose level at 30 minutes post-ingestion (mmol/L)
Evoked Glucose 1	Glucose level at 30 minutes post-ingestion – Glucose level at fasting
1 Hour Glucose	Glucose level at 1 hour post-ingestion (mmol/L)
Evoked Glucose 2	Glucose level at 60 minutes post-ingestion – Glucose level at fasting
Long-term Recovery Glucose	Glucose level at 30 minutes – Glucose level at 2 hours post-ingestion
Slow Rate Recovery Glucose	Glucose level at 60 minutes – Glucose level at 2 hours post-ingestion
2 Hour Glucose Level	Glucose level at 2 hours post-ingestion (mmol/L)
Incremental Area under the Curve	[((g30-g0)/2)*(30-0)] + [{((g30-g0)+(g60-g0))/2}*(60-30)] + [{((g60-g0)+(g120-g0))/2}*(120-60)]
Fasting Insulin	Insulin level at fasting (pmol/L)
QUICKI (Katz et al., 2000)	1/(log(fasting insulin; uU/ml)) + log (fasting glucose (mg/dl)))
ISICOMP (Matsuda et al. 1999)	10000/ √ fasting glucose (mg/dl)* fasting insulin (uU/ml) * mean glucose (mg/dl)* mean insulin (uU/ml)
2 hour Insulin Level	Insulin level at 2 hours post-ingestion (pmol/L)
Beta Cell Function	
1 hour Insulin Level	Insulin level at 60 minutes post-ingestion (pmol/L)
Evoked Insulin 1	Insulin level at 60 minutes post-ingestion – Insulin level at fasting
Slow rate Recovery Insulin	Insulin level at 60 minutes – Insulin level at 2 hours post-ingestion
C peptide Level	Fasting level (pmol/L)
Insulinogenic Index (Uwaifo et al., 2002)	Fasting insulin (uU/ml)/ fasting glucose (mg/dl)
Evoked insulin/Evoked glucose	Insulin level at 60 minutes (pmol/L)/Glucose level at 60 minutes (mmol/L)

(Katz A et al., 2000; Uwaifo et al., 2002). It has been noted that QUICKI is most accurate for relatively normal glycemic and beta cell function levels (Radziuk, 2000), which is appropriate given the present sample of nondiabetic, young adults. ISICOMP was evaluated as it is an index of both, hepatic and whole-body (muscle) insulin sensitivity and has also shown high correlations with the rate of whole-body glucose disposal during the hyperinsulinemic euglycemic clamp ($r = \sim.70$) in a large sample of subjects with varying degrees of glucose tolerance (Matsuda M. & DeFronzo R.A., 1999).

Several indices of beta cell function were also evaluated in the present study. These include fasting, 1-hour insulin levels, and insulin to glucose ratios, which have shown significant correlations with first and second phase insulin release during the hyperglycemic clamp in nondiabetic adults (Stumvoll M et al., 2000). Other measures of beta cell function evaluated also include fasting C peptide, a commonly used as an index of beta cell function and demonstrates strong correlations with steady-phase insulin secretion (Uwaifo et al., 2002) and the insulinogenic index, which has shown superior correlations with first-and steady-phase insulin secretions compared to the homeostasis model assessment of percent B-cell function (Uwaifo et al., 2002).

All the indices that were evaluated are influenced by several factors, including the amount of insulin secreted, the sensitivity of the tissues to insulin, muscle mass, the action of other regulatory hormones such as glucagons, gut hormones, neural stimulation and gastric emptying and absorption (Radziuk, 2000), which determine how glucose is processed by the body. Although, most of these indices, including most measures of insulin sensitivity, are correlated because they are based on metabolic models that utilize

common structural features (Radziuk, 2000; Uwaifo et al., 2002), no index in itself is a pure reflection or summary of the influence of all factors. Furthermore, it is expected that in this sample of healthy young students the variability associated with individual differences in neural stimulation, and gastric emptying and absorption is randomized across the sample and would not significantly interfere or interact with glucoregulatory status.

Individual results were also sent to Dr. Bruyère, a specialist in internal medicine at the Royal Ottawa Hospital for clinical interpretation. More specifically, participants whose glucose values fell within the ranges indicative of type II diabetes as established by the American Diabetes Association, (American Diabetes Association, 2002) were excluded from the study in order to avoid potential cases of diabetes in the sample.

Cognitive Measures

Several measures were administered to ensure a comprehensive evaluation of cognitive function as well as to allow for cross-sectional comparisons of measures. These measures encompassed the following cognitive functions: verbal memory (immediate and delayed); nonverbal memory (immediate and delayed); visuospatial function; attention (auditory and visual); executive/Frontal function; and psychomotor speed. The rationale for choices of the following measures included their previous use in glucoregulatory studies, as well as practical reasons such as simplicity or brevity of administration period and availability. Furthermore, subtests of the WAIS-III (Wechsler, 1997a) and WMS-III (Wechsler, 1997b) were chosen because of their validation, demonstrating high inter-rater and test-retest reliability coefficients as well as construct

and discriminant validity (Wechsler, 1997a, 1997b). These subtests followed standard administration and scoring.

Verbal memory. Given that some studies have demonstrated a relationship between decrements in verbal memory and impaired glucose regulation (S. Craft, Murphy, & Wemstrom, 1994; P. K. Elias et al., 1997; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Perlmuter et al., 1984; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; G M Reaven, Thompson, Nahum, & Haskins, 1990; C. M. Ryan & Geckle, 2000; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; van Boxtel et al., 1998; Vanhanen et al., 1997; Vanhanen et al., 1998; Wahlin, Nilsson, & Fastbom, 2002; Worrall, Moulton, & Briffett, 1993), whereas other studies have not (Desmond, Tatemichi, Paik, & Stern, 1993; Grodstein, Chen, Wilson, & Manson, 2001; Kilander, Nyman, Boberg, & Lithell, 1997; Lowe, Tranel, Wallace, & Welty, 1994; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Scherr et al., 1988; Vanhanen et al., 1999; Zaslavsky, Gross, Chaves, & Machado, 1995), several verbal measures were included to ascertain this relationship as well as to determine whether contextual verbal memory measures are more sensitive than noncontextual measures to glucoregulatory effects in a young nondiabetic population. Three measures were administered to evaluate these factors. The contextual verbal memory task selected for this study is the Logical Memory subset of the Wechsler Memory Scales-III (WMS-III; (Wechsler, 1997b), which involves recall of a short story. This instrument has been chosen to allow for

comparisons with the multiple other studies that have used a similar measure (Atiea, Moses, & Sinclair, 1995; Cosway, Strachan, Dougall, Frier, & Deary, 2001; S. Craft, Murphy, & Wemstrom, 1994; P. K. Elias et al., 1997; Grodstein, Chen, Wilson, & Manson, 2001; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Jagusch, v. Cramon, & Hepp, 1992; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; Lowe, Tranel, Wallace, & Welty, 1994; C A Manning, Hall, & Gold, 1990; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Messier, Gagnon, & Knott, 1997; Parsons & Gold, 1992; C. M. Ryan & Geckle, 2000; Scherr et al., 1988; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990).

Although the content and scoring of this measure was standard, its presentation and the response recording were modified. Stories A and B were counterbalanced across subjects so that during the second session, half the subjects received Story A, and the other half, Story B. The alternate story was administered in the third session. In total, three verbal recalls were obtained from subjects per session: one immediately following the first presentation of the story, another following a second presentation of the same story that took place immediately after the first recall, and the third, 25-35 minutes following the second recall. Each given story was presented on a recording as opposed to being presented by the tester. This procedure allowed for control of the speed of presentation of each story for each participant. It has been previously observed, using the Logical Memory subtest of the WMS-R (Wechsler, 1987), that recall of the story units are dependent on the speed of presentation of the stories (Shum, Murray, & Eadie, 1997). More specifically, college students in the "fast" presentation group recalled fewer words than those in the "slow" presentation group. Prior to each paragraph presentation,

subjects were asked to try to remember as much information as they could on the test and following the second recall, subjects were also instructed to memorize as much of the story as they could because they would be required to recall the story again later. In order to ensure that all recall units were recorded, the participants' verbal recalls were audio taped. Units of information were determined for each recall according to the standardized coding of the WMS-III (Wechsler, 1997b). The resulting scores were expressed as a percentage of the total units to be recalled for each story.

The second test is a Verbal Free Recall test comprised of a practice list of 12 words and four experimental lists of 20 words equated on five variables: word frequency (M = 214 occurrences per million), imagery-evoking value (M = 4.67 on a 7-point scale), number of word letters (M = 5.32), number of phonemes (M = 4.17), and number of syllables (M = 1.5). The third test is an Order Reconstruction task that 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 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 words in the Verbal Free Recall and Order Reconstruction Tasks appeared individually at the center of a SVGA video monitor, in white upper-case letters on a black background. Viewing distance was approximately 70 cm. Timing, randomization and presentation of the list words were controlled by a PC-compatible microcomputer and the Micro Experimental Laboratory

(MEL) software, Version 2.0 (Schneider, Rodgers, Mciejczyk, Zuccolotto, & St-James, 1995).

For the Verbal Free Recall task, subjects were informed that they would see four lists of individual words to study and that each list was followed by a 2-min recall period, which was announced by an auditory cue immediately after the last list word. They were instructed to try to recall as many words as they could during that period and that they could recall words in any order. During the study phase, each word was displayed for 1.5 s with an interstimulus interval of 200 ms. The order of the four lists and that of words within lists were randomized. Four individual scores, three of which were based on the serial position of the words in the presentation lists, were computed from the free-recall data: a total recall score, a primacy-position score, a middle-position score, and a recency-position score. The primacy and recency scores were calculated, respectively, using the first and last five word positions of the presented list. The middle scores were calculated from the 10 words in the middle of the presented lists. These scores were calculated given the observation that glucoregulatory effects appear to interact with serial position of words in recall lists (Messier, Desrochers, & Gagnon, 1999).

Following the Verbal Free Recall task, subjects were presented with the Order Reconstruction task. They were informed that they would see one practice list of 12 words and 2 experimental lists of 20 words each. As with the Verbal Free Recall task, the order of the two experimental lists and that of words within lists were randomized. The procedure used for list presentation was the same as that of the verbal free recall task. 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 was that subjects had to recall the

order of presentation of each word. To that effect, they were shown the list of words in alphabetical order on a sheet of paper with numbered lines and were given 2 minutes to rewrite the words in the correct order. A single recall score was obtained from this task. This measure was defined as the average percentage of words recalled in their correct positions.

Nonverbal memory. This function was evaluated using the Rey Complex Figure Test and the Taylor Figure Test as the alternate test. Similar to the paragraph recall measure (Logical Memory), administration of these figures was counterbalanced: half the subjects received the Rey Complex Figure first and the other half, the Taylor Figure first. The alternate figure was administered during the third session. This test involves immediate reproduction, by drawing, of a complex figure 3 minutes and 30 minutes following its copy (see visuospatial function below). The complex figure was chosen because it has been extensively used to evaluate nonverbal memory and has been shown to have good interscorer reliability ($r > .90$; (Berry, Allen, & Schmitt, 1991; Shorr, 1992). The recall trials have been shown to have strong visual memory components (Loring, Lee, & Meador, 1988) as well as strong visuospatial components (Berry, Allen, & Schmitt, 1991).

Visuospatial function. Although studies evaluating glucoregulatory effects have shown that visuospatial function does not appear to be sensitive to the effects of impaired glucose regulation (Assisi et al., 1996; Cerizza et al., 1990; Cosway, Strachan, Dougall, Frier, & Deary, 2001; Dey, Misra, Desai, Mahapatra, & Padma, 1997; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Kilander, Nyman, Boberg, & Lithell, 1997; Lindeman et al., 2001; Lowe, Tranel, Wallace, & Welty, 1994; Mattlar, Falk, Rönnemaa,

& Hyyppä, 1985; Meuter, Thomas, Gruneklee, Gries, & Lohman, 1980; G M Reaven, Thompson, Nahum, & Haskins, 1990; C. M. Ryan & Geckle, 2000; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998; Vanhanen et al., 1997; Vanhanen et al., 1999), this function was evaluated to further ascertain such observations using a larger sample. The copy trial of the Complex Figure Test was used to evaluate visuospatial function. More specifically, participants were asked to reproduce, by drawing, the complex figure placed in front of them. It consists of geometrical shapes and details within a rectangle/square mainframe, resulting in 18 separate evaluative units. Each unit is scored according to its accuracy and placement (Awad et al., 2004; Meyers & Meyers, 1995). There was no time limit for this task. This task has been shown to be sensitive to visuospatial difficulties and perceptual fragmentation in patients with right hemisphere damage (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004).

Attention. Attentional function was assessed using auditory and visual measures. Auditory attention was assessed with the Digit Span subtest of the WAIS-III (Wechsler, 1997a) to allow for comparisons with previous glucoregulatory studies (Assisi et al., 1996; Atiea, Moses, & Sinclair, 1995; Cerizza et al., 1990; Dey, Misra, Desai, Mahapatra, & Padma, 1997; P. K. Elias et al., 1997; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992; Kilander, Nyman, Boberg, & Lithell, 1997; Lindeman et al., 2001; Lowe, Tranel, Wallace, & Welty, 1994; C A Manning, Hall, & Gold, 1990; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Messier, Gagnon, & Knott, 1997; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Perlmuter et al., 1984; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; G M Reaven, Thompson, Nahum,

& Haskins, 1990; Scherr et al., 1988; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; Vanhanen et al., 1997; Zaslavsky, Gross, Chaves, & Machado, 1995). Its administration and scoring followed standard procedure. Participants were asked to repeat strings of numbers (up to nine numbers), immediately following their auditory presentation (1 number per second; Digit Span Forward). For the second part of the Digit Span test, participants were asked to repeat strings of numbers (up to eight numbers) in the reverse order they were presented (Digit Span Backward). Participants are presented with two sequences for each given span. When at least one of two sequences of a given span are repeated correctly, the examiner reads the next longer number sequences, until the participant fails a pair of sequences. Digit Span Forward has been shown to be more closely related to the efficiency of attention than to memory (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Patients who show evidence of diffuse brain damage (e.g., mild head trauma, multiple sclerosis) tend to repeat the correct digits, however mix up the order, which suggests attentional difficulties (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Digit Span Backward has been described as a more complex test of attention, requiring mental tracking (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Participants are required to briefly store the numbers while juggling them mentally to reverse their order. Digit Span Backwards has been shown to be sensitive to left-hemisphere function and dementia (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004).

Another test of complex attention is the Letter-Number Sequencing subtest of the WAIS-III (Wechsler, 1997a). Participants are presented with letters and numbers (up to eight letters and numbers) that they are asked to repeat starting with the numbers in

ascending order followed by the letters in alphabetical order. These are presented verbally at a rate of one number or letter per second. Participants are presented with three sequences for each given span of numbers and letters. When at least one of three sequences of a given span are correctly ordered, the examiner reads the next longer sequences, until the participant fails all three sequences of a given span. This test is similar to the Digit Span Backward in that it also requires mental shuffling of stimuli, however, it appears to require additional attentional capacity given that two independent sets of stimuli are needed to be shuffled. This test was chosen as a reliable test of complex attention that would allow for comparisons with the simpler measures of auditory attention (Digit Span Forward) in order to determine the more sensitive attentional functions to glucoregulatory effects.

Complex attention and working memory were also be evaluated using the Arithmetic subtest of the WAIS-III (Wechsler, 1997a). This test consists of 20 arithmetic problems requiring simple to more complex arithmetic solutions that are solved mentally (i.e., no written calculations permitted). Participants are required to provide the correct answer within a given time period which varies (30 seconds to 2 minutes) depending on the difficulty of the question. This test is discontinued following four consecutive incorrect responses. This test was included because of the numerous glucoregulatory studies that have evaluated arithmetic function and yielded inconsistent findings : One study demonstrated a relationship between arithmetic function and glucoregulatory status (U'Ren, Riddle, Lezak, & Bennington-Davis, 1990), while others did not (Atiea, Moses, & Sinclair, 1995; Cerizza et al., 1990; S. Craft, Murphy, & Wemstrom, 1994; Dey, Misra, Desai, Mahapatra, & Padma, 1997; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985).

Futhermore, it appears to require different attentional abilities compared to the other tests that were evaluated. The resolution of timed oral arithmetic problems appears more likely to involve concentration, immediate memory as well as verbal functions and less likely to reflect arithmetic skill (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Given that there appears to be important practice effects on this measure in which a particular solution is likely to be remembered on the subsequent session, an alternate version was created and was assessed for its comparability with the original subtest using the large study sample. Half the participants received the original version during the second session and the other half, the alternate version. The alternate forms were administered during the third session.

Visual attention was evaluated using the Spatial Span subtest of the WMS-III (Wechsler, 1997b). Given that only few studies have evaluated this function and that a relationship between visual attention and glucose regulation was not observed (Assisi et al., 1996; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Kilander, Nyman, Boberg, & Lithell, 1997; Messier, Gagnon, & Knott, 1997), the Spatial Span subtest was used to ascertain past findings. Furthermore, results of this test would allow for comparisons with auditory attention, more specifically Digit Span (Forward and Backward) to determine whether glucoregulatory effects are observed across both attentional modalities (auditory and visual) and across both simple (Forward subtests) complex (Backward subtests) measures of attention span. The Spatial Span subtest follows a similar procedure as the Digit Span subtest in that participants are presented with an increasing number of stimuli (visual for this test) that they are asked to repeat in the same order (Spatial Span Forward) or in the reverse order (Spatial Span Backward).

The stimuli consist of 2 cm^3 blue cubes fixed randomly on a 20-cm^2 board. The examiner touches the cubes in a predetermined order, at a rate of 1 cube per second. Spatial span has been shown to be specific to visual field defects and not anterograde amnesia reflecting its specificity to visual attention (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004).

Executive/Frontal lobe function. Given the inconsistent findings of glucoregulatory studies evaluating executive function (Allen, Gross, Aloia, & Billingsley, 1996; Atiea, Moses, & Sinclair, 1995; Cerizza et al., 1990; Cosway, Strachan, Dougall, Frier, & Deary, 2001; S. Craft, Murphy, & Wemstrom, 1994; Desmond, Tatemichi, Paik, & Stern, 1993; Dey, Misra, Desai, Mahapatra, & Padma, 1997; P. K. Elias et al., 1997; Grodstein, Chen, Wilson, & Manson, 2001; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; Kilander, Nyman, Boberg, & Lithell, 1997; Lindeman et al., 2001; Lowe, Tranel, Wallace, & Welty, 1994; C A Manning, Hall, & Gold, 1990; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Parsons & Gold, 1992; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; G M Reaven, Thompson, Nahum, & Haskins, 1990; C. M. Ryan & Geckle, 2000; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; van Boxtel et al., 1998; Vanhanen et al., 1997; Vanhanen et al., 1999; Wahlin, Nilsson, & Fastbom, 2002), one measure of executive function was used in this study to further assess the sensitivity of executive function to glucoregulatory effects. It is a variant of the Brown-Peterson technique (Peterson & Peterson, 1959). It consists of three conditions: Baseline, Delay and Interference conditions. In all three conditions, participants hear three consonant letters, at a rate of one letter per second that they are

required to recall in writing following an auditory cue. For the Baseline condition, participants are required to recall the letters immediately following their presentation. For the Delay condition, participants are required to recall the letters after a 20-second delay. For the Interference condition, participants are required to recall the letters after a 20-second delay under conditions of interference. More specifically, in the latter condition, participants hear the three consonant letters followed by a 3-digit number. Immediately after hearing the number, participants are required to begin counting backwards, out loud by threes, until they heard an auditory cue (after the delay of 20 seconds). Participants are then asked to stop counting and recall the three consonant letters in writing. A total of 4 practice and 10 experimental trials were administered for each condition. The randomization of the letters and three digit numbers was controlled by a PC-compatible microcomputer and the Micro Experimental Laboratory (MEL) software, Version 2.0 (Schneider, Rodgers, Mciejczyk, Zuccolotto, & St-James, 1995).

For the purpose of this study, only data from the Interference condition was used to evaluate executive function. The Interference condition requires divided attention as well as mental tracking of each of the two functions (counting and short-term retention of letters). Such interference tasks have been shown to be sensitive to head injury patients (Stuss et al., 1985) as well as to frontal lobe and left hemisphere function (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). The Baseline and Delay conditions provided a measure of methodological control to ensure that the performance observed on the Interference condition was independent of basic auditory (Baseline condition) and sustained attention (Delay condition). Performance of participants on these two conditions indeed showed ceiling effects (see Results), suggesting that their performance

on the interference condition appears to be a reflection of their executive function and not of basic or sustained attention. Total number of correctly recalled triads were evaluated for this measure.

Psychomotor speed. Two measures of psychomotor speed were used in this study: Digit Symbol Coding and Symbol Search subtests of the WAIS-III (Wechsler, 1997a). These measures as well as other comparable measures have also been consistently used in glucoregulatory studies (Allen, Gross, Aloia, & Billingsley, 1996; Atiea, Moses, & Sinclair, 1995; Cerizza et al., 1990; Cosway, Strachan, Dougall, Frier, & Deary, 2001; Desmond, Tatemichi, Paik, & Stern, 1993; R T Donohoe & Benton, 2000; Jagusch, v. Cramon, & Hepp, 1992; Kilander, Nyman, Boberg, & Lithell, 1997; Lindeman et al., 2001; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Messier, Gagnon, & Knott, 1997; Meuter, Thomas, Gruneklee, Gries, & Lohman, 1980; G M Reaven, Thompson, Nahum, & Haskins, 1990; C. M. Ryan & Geckle, 2000; Tun, Perlmuter, Russo, & Nathan, 1987; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; van Boxtel et al., 1998; Vanhanen et al., 1997; Vanhanen et al., 1999). The findings to date have yielded inconsistent conclusions, thus their evaluation allowed further assessment of their sensitivity to glucoregulatory effects. Digit Symbol Coding consists of 7 rows, containing 133 blank squares. Above each blank square is a random number from 1 to 9. Above these rows is a printed key that pairs each number, presented in the correct order, from 1 to 9, with a different nonsense symbol. Following a practice trial on the first seven squares, the task is to fill in the blank squares with the correct associated symbol as quickly as possible for 120 seconds.

Symbol Search requires participants to visually scan two groups of symbols: a target group (composed of two symbols) and a search group (presented to the right of the target group and composed of five symbols) and to indicate, by marking either a "Yes" or "No" box, depending on whether either of the target symbols matches any of the symbols in the search group. The participant responds to as many target groups (maximum of 60) within a 120-second limit. Performance on such tasks has been shown to involve motor persistence, sustained attention, response speed and visuomotor coordination (Schear & Sato, 1989) and appears unaffected by memory or learning (Erber, Botwinick, & Storandt, 1981). It has also been shown that such psychomotor speed tasks are particularly sensitive to diffuse brain damage in that performance decrements are observed even with minimal damage or simple aging (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Furthermore, given the sensitivity of such tasks to attention and mild brain dysfunction, they have been employed to verify other transient states affecting brain function such as hypertension and have been reliable in demonstrating treatment-associated improvements in function (Miller, Shapiro, King, Ginchereau, & Hosutt, 1984).

The scoring of the measures was conducted by two research assistants blind to the condition of the participants. Assistants were trained by a neuropsychologist using standard scoring criteria (when available) or the above-described operationally defined scoring criteria.

Procedure

In total, data collection involved three testing sessions. All instructions for the testing sessions were provided in a written format to ensure adherence to the research

protocol (see Appendix E for Test Administration and Sessional Instructions). The three sessions were scheduled, approximately 1 week apart, to ensure that all participants receive comparable testing procedures. In addition to the three testing sessions, one glucose screening session was introduced for a subset of participants for the purpose of recruiting females whose blood glucose levels reflected relatively poorer glucose regulation.

Screening session. This session was included in the recruitment of the last 20 female subjects. Preliminary statistical analyses of females' peak blood glucose levels (n = 50), typically observed at 30 minutes post glucose injestion (75 g. of glucose; Glucose tolerance test), had revealed a relatively homogenous group of glucoregulators: Only approximately 25 % of females had peak glucose levels greater than 8.1 mmol./L, which is lower than what has been typically associated with glucoregulatory effects (9.0 mmol/L; (Gonder-Frederick et al., 1987; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Carol A. Manning, Parsons, Cotter, & Gold, 1997; C. A. Manning, Parsons, & Gold, 1992; C. A. Manning, Stone, Korol, & Gold, 1998; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997). Given the small number of females with relatively poorer glucose regulation, a glucose screening procedure was incorporated to recruit only females who showed relatively higher peak glucose levels. High peak glucose was operationally defined as 30-minute glucose levels, following injestion of a 75g glucose solution, greater than the upper quartile of the initial sample (8.1 mmol/L.). The upper quartile of the initial sample was chosen as the more reliable glucose index because it was obtained from a sample of comparable

demographics. Analyses of males' 30-minute post-injestion glucose levels (n = 54) revealed a greater range compared to females' 30-minute post-injestion glucose levels: approximately 25 % of males had glucose levels higher than 8.9 mmol/L compared to 8.1 mmol/L for females whereas approximately 25% of males' and females' glucose levels were lower than 6.0 mmol/L. Given the greater range in males' glucose levels and that the upper quartile of males' glucose level is closer to peak levels associated with glucoregulatory effects (Gonder-Frederick et al., 1987; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Carol A. Manning, Parsons, Cotter, & Gold, 1997; C. A. Manning, Parsons, & Gold, 1992; C. A. Manning, Stone, Korol, & Gold, 1998; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997), the screening procedure was not employed for male participants. Although the introduction of this screening session for a subsample of the female subjects is likely to introduce bias given the differential recruitment strategies, the importance of ensuring a wide range of glucose regulation was necessary to obtain additional power and surpasses the potential bias. Furthermore, following the screening session, these females underwent the same methodology (i.e., counterbalancing of solutions/forms) as the entire sample, thus the extent of bias is expected to be minimal.

The screening session was scheduled in the mornings to ensure fasting status. Informed consent for the screening session was obtained (see Appendix F for Glucose Screening Consent Form). Three glucose samples were collected during this session: Fasting, 15-minute and 30-minute post-glucose ingestion. Blood glucose was measured using a Glucolet lancet (Bayer Canada, Toronto, Ontario, Canada). One drop of blood

was obtained and measured with an Elite Glucometer (Bayer, Canada; (Messier & Kent, 1995). The glucose solution consisted of a 296 ml. lemon-flavored beverage (Cool Aid flavoring without glucose added) containing 75 g of glucose, consistent with the glucose beverage of the Glucose tolerance test (see above). Participants whose 30-minute post-glucose injestion levels were greater than the sample's upper quartile (8.1 mmol/L) were informed that their glucose level met the research criteria and were invited to participate in the remainder of the study. The research protocol following the screening session was comparable for all participants who completed the study. Participants whose glucose values fell below the sample's upper quartile were informed that their glucose level did not meet the research criteria and were thanked for their participation. At the end of the session, all participants obtained $5 for their participation in the screening session. This session lasted approximately 40 minutes.

First session. This session was scheduled in the morning between 8 and 9 a.m. and lasted for approximately 2.5 hours. The first part of the session was conducted in a quiet testing room at the University of Ottawa. Upon arrival to the memory laboratory, informed consent was obtained from each participant after the nature and possible consequences of the study were explained and the participants' questions and/or concerns addressed (see Appendix F for General Consent Form). The tester then asked the participant whether he or she had been fasting from midnight in order to obtain some confirmation of a fasting state. Fasting glucose levels can also substantiate reported fasting states.

Participants were asked about smoking history, frequency of exercise (recorded as average minutes of exercise per week) and history of diabetes in either parent. Their

height and weight were also measured to provide an accurate estimate of body mass index (kg/m^2). Information on these factors was obtained given their identification as associated risk factors for altered glucoregulation (Eriksson & Lindgaerde, 1996; Shaten, Smith, Kuller, & Neaton, 1993). Participants were also asked the number of years of education completed. One year of part-time education were operationally defined as 0.5 years of full-time education.

Finally, the Beck Depression Inventory (Beck, 1987) was administered and the second session scheduled. The participant was informed that he or she was also required to fast using the same fasting protocol for the second and third sessions. The participant was then accompanied to University of Ottawa's Health Center Laboratory for the administration of the glucose tolerance test and blood sampling to obtain biological data.

Second and third sessions.

This part of the study follows a double-blind repeated measures design in which each participant was tested under both glucose and saccharin conditions, thus serving as his or her own control. The second and third sessions followed the same procedure with the exception that participants received the alternate solution on the third session. These sessions were conducted in the same testing room that was used for the first session and lasted approximately 1 hour and 45 minutes. They were scheduled at a time, in the morning, most convenient for the participants. The overall procedure and order of administration of the measures is presented in Table 2.

To insure compliance to the fasting instructions, participants' glucose levels were measured using a Glucolet lancet (Bayer Canada, Toronto, Ontario, Canada). One drop

Table 2
Assessment Procedure of Second and Third Sessions

Glucose Measurement (Fasting)
Ingestion of Solution
Arithmetic
Digit Symbol Coding
Modified Brown Peterson Task
Symbol Search
Digit Span (Forward and Backward)
Paragraph Recall-Immediate Recalls
Figure-Copy
Glucose Measurement (1 hour)
Figure-Immediate Recall
Verbal Free Recall
Paragraph Recall-Delayed Recall
Letter-Number Sequencing
Figure-Delayed Recall
Order Reconstruction Task

of blood was obtained and measured with an Elite Glucometer (Bayer, Canada; (Messier & Kent, 1995), similar to the sampling procedure used in the screening session. Another glucose measurement was obtained 60 minutes following the ingestion of the solution to ensure solution effects.

At the beginning of the sessions, each participant ingested a 240 ml. lemon-flavored (Cool Aid flavoring without glucose added) beverage containing either 50g of glucose or 50.4 mg of saccharin. These doses were selected because of their association to the previously observed hyperglycemic facilitative effect on memory performance in young participants (S. Craft, Murphy, & Wemstrom, 1994; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997). Furthermore, in order to ensure that both solutions have comparable tastes, saccharin (4 mg) were added to the glucose solution (Messier, Desrochers, & Gagnon, 1999). The administration of the solutions

was determined by a randomized procedure in which each participant had an equal probability of obtaining either solution on the first visit.

Five minutes following ingestion of the glucose or saccharin solution, participants were administered the battery of tests. This 5-minute time interval between ingestion and cognitive testing is the interval that has previously used in procedures demonstrating hyperglycemic facilitation (Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997).

In the event that participant's glucose level reaches 2.5 mmole/l or less or if the participant reports weakness or dizziness, he or she would be given a 100 ml drink containing 20% glucose to raise their blood glucose. Blood glucose would be monitored until normal levels would be achieved before dismissing the participant. This, however, did not occur for any participant enrolled in the study.

At the end of the third session, participants were asked whether they could identify the solution ingested during the session and this data was used to ensure whether participants were indeed blind to the solutions ingested. Participants received 20$ for their participation.

Results

Overview of Statistical Analyses

The primary purpose of this study was to determine the relationship between measures of cognitive function and glucose regulation in a large sample of young nondiabetic adults. To this end, an important objective was to establish a reliable biological marker of cognitive decrements associated with impaired glucoregulation. Furthermore, given the association of vascular disease and hyperinsulinemia, it was also

important to determine the relative contribution of vascular risk factors to the cognitive decrements observed in nondiabetes patients with poorer regulation.

Several statistical analyses were conducted in an aim to achieve these objectives. Initially, all highly correlated variables were statistically reduced into meaningful clusters (Wahlin, Nilsson, & Fastbom, 2002). Specifically, principal components factor analyses were conducted on the glucoregulatory indices (including c-peptide levels) for the purpose of reducing the number of statistical comparisons conducted (and minimize the probability of committing type I error). In addition, principal components factor analyses were also conducted on the vascular risk factors (Total cholesterol, HDL and LDL cholesterol, HDL cholesterol/Total cholesterol ratio and total triglycerides) and on the cognitive measures to determine how these factors are clustered and to determine variable groupings for subsequent analyses.

Hierarchical linear regressions were then conducted to evaluate the relative contribution of glucoregulatory indices and vascular factors to the various cognitive factors. These analyses were designed to determine the independent contribution of age and education, cardiovascular risk factors and glucoregulatory factor scores as well as to determine the cognitive variation associated with glucoregulation, after the variation associated with demographic variables and cardiovascular risk factors had been accounted for.

It was also important to determine whether glucose differentially interacts with varying levels of glucose regulation (better, average, worse regulation) as well as whether the effects of glucose regulation differ for males and females. For the purpose of evaluating gender differences and glucose effects on the performance of better, average

and worse glucoregulators, the distinction between better, average and worse regulators was determined using the glucoregulatory factor score most consistently associated with cognitive function. More specifically, the extreme quartiles of the sample were determined using the distribution of this glucoregulatory index and were identified as the better/worse regulators. The remaining participants were identified as average regulators. This procedure of separating the sample into extreme groups (better and worse regulators) has been previously used with young populations (R. T. Donohoe & Benton, 1999; Martin & Benton, 1999) and may be necessary in determining potential differences in a young healthy sample in which it is more difficult to observe impaired glucose regulation. Data obtained from the middle group (average regulators) could be useful in identifying the progression of glucoregulatory effects. Although the distinction between better, average and worse regulators is relative and dependent on the sample obtained, limiting generalizability, the specific glucoregulatory values associated with the two groups will be provided to allow for comparisons across studies.

The analyses evaluating gender differences and hyperglycemic effects on cognitive function involved a quasi-experimental design for the participants were not randomly assigned to the glucoregulatory or gender group. However, each participant had an equal chance of ingesting either, the glucose or saccharin solution, thus, ensuring manipulation effects. The analyses were conducted using repeated multiple analysis of variances (MANOVAs), in which the dependent variables (cognitive measures) for each analysis were determined based on their factor clustering. This reduced considerably the number of analyses conducted and the probability of committing type I error. Independent between-subjects variables included glucoregulatory group (better, average

and worse regulators) and gender (male versus female). The repeated measure was the solution ingested (glucose versus saccharin). The order of solution ingestion (glucose at the first assessment and saccharin at the second assessment versus saccharin at the first assessment and glucose at the second assessment) was randomly assigned and counterbalanced across the two assessments, and thus, was not expected to systematically affect the results. Furthermore, practice effects resulting from the first assessment were minimized as a result of the repeated measures design and the counterbalancing of the cognitive measures and solutions.

In addition to the main factorial analyses, either chi-square analyses (for dichotomous variables) or one-way analyses of variance (ANOVA for continuous variables), were conducted to compare the groups on measures of glucose regulation, measures of vascular risk factors as well as on other risk factors associated with altered glucose regulation. These included smoking history frequency of exercise (minutes per week), and body mass index. Comparisons were also conducted to determine the effects of the different methodologies employed to obtain c-peptide and insulin measures as well as to ensure solution effects (glucose levels during saccharin versus glucose conditions), comparability of alternative cognitive measures, and that participants were indeed blind to the solutions ingested.

An attempt was made to ensure that all the statistical assumptions for these analyses were met. More specifically, the sample sizes employed for all the analyses were sufficiently large to conduct all the analyses (factorial, regression and factor analyses) (Bryant & Yarnold P.R., 1995; Hatcher, 1994; Tabachnik & Fidell, 1996). In addition, appropriate data type (i.e., continuous or interval data) was also ensured for

these analyses. For the factor analyses, the correlations among the variables were sufficiently high to ensure valid factor clustering and the resulting factors showed face validity (see Results and Discussion). For the regression analyses, the observations were independent, the data were unbounded or unrestricted and the statistical software (SPSS, version 12) ensured that perfect multicollinearity was avoided (see Results for details). For the factor and regression analyses, the data set was sufficiently large to minimize the impact of nonlinear/skewed distributions.

In the repeated MANOVAs, all independent variables were categorical and all dependent variables were continuous/interval. Corrections for unequal sample sizes per cell were automatically conducted by the statistical software (SPSS). Given that relatively smaller samples resulted each of the MANOVA cells, multivariate normality was evaluated for each cell and each variable analyzed. Outliers in each cell, identified as values smaller or greater than 3 standard deviations were replaced by the values reflecting $\pm$ 3 standard deviations of the distribution for the given cell. This procedure was conducted to avoid excluding complete subject data because of isolated extreme values. It also ensured that the replacement values reflected the magnitude and direction of the original values (Tabachnik & Fidell, 1996). Only isolated extreme values were identified, and the statistical findings of the original and the transformed data were essentially identical (see below Results for details).

Given that several statistical analyses were conducted and that important implications could be potentially associated with poorer glucose tolerance, including poorer neuropsychological functioning (S. Craft, Murphy, & Wemstrom, 1994; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990;

Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997), an attempt was made to highlight patterns of concordance in the results obtained from the various analyses. In addition, several attempts were made to control for type I error. These included the use of factor analyses to reduce the number of variables evaluated, the use of MANOVAs to reduce the number of statistical analyses conducted as well as ensuring large samples for the analyses. Given these attempts and that only hypothesized and convergent findings will be emphasized, the alpha level to identify statistically significant differences was set at .05, although most relevant findings were observed at alpha levels below .01. All the analyses were conducted using SPSS (version 12). For post-hoc comparisons, the Tukey's honestly significant difference (HSD) was used as a conservative measure of post-hoc differences.

Sample Characteristics

Of the total 68 males and 75 females, who met the criteria for the study, only 8 males and 5 females discontinued following the first visit (blood testing-glucose tolerance test). Although most participants described the glucose tolerance test as long, none reported significant discomfort or side effects. An additional 7 participants (3 males; 4 females) did not complete the final cognitive assessment. Participants who discontinued reported scheduling difficulties (exam periods, assignments, or illness) or did not show up to at least two subsequent scheduled visits. One female met criteria for depressive symptomatology, scoring within the moderate range of the Beck Depression Inventory, and her data were excluded from all analyses. In total, 57 males and 65 females completed all three visits (blood testing and both cognitive assessments). In addition to participant drop-outs, random experimenter, equipment (computer/hardware),

or laboratory (blood sampling and measurement) errors resulted in isolated missing data points, which were reflected by the small variations in sample sizes reported. Data of participants, who completed at least the first cognitive assessment, were included in all the analyses except for the repeated MANOVAs, which required both cognitive assessments. The sample size for this study was deemed sufficient (Cohen, 1988) for most analyses (i.e., ANOVAs; Chi Square; Correlations; Multiple Regression; Factor Analyses), with the exception of some of the MANOVA groups, which were smaller than anticipated. Sample size was determined on the basis of power calculations using estimated medium effect sizes, noted in past similar studies (Messier, 1997; Messier, Desrochers, & Gagnon, 1999). The implications of relatively small samples in the MANOVA analyses were addressed in the Discussion section.

Within the sample of participants who completed at least one cognitive assessment, none met criteria for diabetes mellitus, nor for impaired fasting glucose, however, 8 subjects (4 males; 4 females) met criteria for impaired glucose tolerance (IGT; (American Diabetes Association, 2002, 2006). These IGT subjects were not excluded from the analyses as their glucose levels reflect the more extreme cases within the continuum of glucose regulation and would likely contribute to important differences between better and worse glucose regulators.

Analyses Ensuring Methodological Control

Effects of participant blindness to solution ingested. As many as 57% of participants correctly identified the solutions ingested during the cognitive assessments, which was unlikely due to chance, χ^2 (1, N = 119) = 17.02, $p < .000$. One-way ANOVAs were thus conducted to determine whether participants who correctly identified the

solutions differed in their cognitive performance to participants who incorrectly identified the solutions. These findings revealed no significant differences on any measure between the groups (all *ps* > .05), suggesting that the knowledge of solution ingested did not likely affect cognitive performance.

Differences in the analysis techniques of c-peptide and insulin. One-way ANOVAs were conducted to determine whether the two methods employed (radioimmunoassay versus chemiluminescent immunoassay) to determine c-peptide and insulin levels were comparable. The analyses revealed that the radioimmunoassay technique yielded significantly lower c-peptide levels, $F(1, 126) = 13.67$, $p < .000$ and significantly higher fasting, $F(1, 127) = 38.72$, $p < .000$, 60 minute, $F(1, 125) = 8.79$, $p < .005$ and 120 minute insulin levels, $F(1, 125) = 7.75$, $p < .01$; see Table 3 for means). Given that there were no repeated-measures data, in which each c-peptide and insulin sample was compared using both techniques, adjustments or corrections for these values were not possible. Although, no adjustments are made for the use of either technique in determining clinical reference ranges, and that the use of either technique across the samples was unsystematic, the possible impact of these differences in the results was highlighted.

Comparability of alternate cognitive measures. Comparisons were also conducted to ensure that alternate test forms were comparable for the sample employed. The ANOVAs revealed that the alternate test for the Arithmetic subtest of the WAIS-III was comparable to its original form, $F(1, 127) = .96$, $p > .05$, however, performance on the

Table 3
Mean Differences (+ SE) between the Two Analysis Techniques for C-peptide and Insulin

	Index			
Technique	C-peptide	Insulin (fasting)	Insulin (60 minutes)	Insulin (120 minutes)
Radioimmunoassay (n = 56-58)	629.99 (30.85)*	129.74 (10.25)*	625.70 (47.23)*	472.36 (37.48)*
Chemiluminescent Immunoassay (n = 70-71)	886.99 (57.12)	64.76 (4.37)	458.37 (33.43)	335.10 (32.32)

Note. * $p < .006$: Difference between the techniques

two paragraph recall stories (Story A versus Story B of the paragraph recall subtest of the WMS-III) was not comparable for their immediate recall at the first , $F(1, 127) = 31.21$, $p < .000$, and second presentations, $F(1, 127) = 23.58$, $p < .000$, and their delayed recall, $F(1, 127) = 24.07$, $p < .000$. Story A appeared easier to recall compared to story B. Similarly, performance on the two complex figures (Rey Complex Figure and Taylor Figure) yielded significant group differences in their immediate, $F(1, 127) = 13.54$, $p < .000$ and delayed recalls, $F(1, 127) = 10.87$, $p < .01$: The Taylor figure appeared to be easier recalled compared to the Rey complex figure (see Table 4 for means). The potential interactive effect (with glucoregulatory status/gender) of the differing alternate tests could not be evaluated due to the resulting small samples (which would be caused by dividing samples in half). However, given that the order of test assignment was randomly determined and was counterbalanced across all subjects, differences in alternate test performance were not expected to systematically confound that data. Furthermore, as noted above, conclusions were determined on the basis of convergent findings and not isolated significant differences.

Glucoregulatory, Vascular and Neuropsychological Factor Clusters

Glucoregulatory factor clusters. A principal components factor analysis with varimax rotation on the glucoregulatory indices (including c-peptide levels) was conducted to reduce the number of variables into meaningful clusters (see Table 5 for results). All data from subjects who had completed at least the first cognitive assessment were included in this analysis. This ensured that the resulting factor scores, which were used in the subsequent regression analyses (see next section for details), were based on the same participants. In summary, this analysis yielded five factors with eigenvalues

Table 4
Mean Differences (+ SE) between Alternate Test Forms used in the Cognitive Assessment

	Cognitive Tests	
Measures	Logical Memory (WAIS-R) Story A n = 65	Story B n = 64
Immediate Recall-1	63.69 (1.67)*	50.80 (1.60)
Immediate Recall-2	84.43 (1.20)*	74.56 (1.65)
Delayed Recall	81.54 (1.22)*	71.94 (1.53)
	Figures Rey Complex Figure n = 65	Taylor Figure n = 64
Copy	33.26 (0.31)	32.81 (0.28)
Immediate Recall	22.64 (0.75)*	26.13 (0.58)
Delayed Recall	22.85 (0.71)*	25.78 (0.53)

Note. * $p < .001$: Difference between alternate forms.

Table 5
Principal Components Factor Structure of the Glucoregulatory Indices (n = 126-129)

Indices	Factors				
	1-Evoked glucose	2-Beta cell function/Insulin sensitivity	3-Evoked insulin	4-Glucose absorption	5-Basal function
AUCg	**0.95**	0.05	0.08	-0.25	-0.05
Evoked Glucose 2	**0.94**	0.08	0.04	-0.18	0.02
1 hour Glucose	**0.93**	0.10	0.02	-0.15	0.18
Evoked Glucose 1	**0.89**	-0.04	0.19	0.17	-0.08
30-minute Glucose	**0.89**	-0.02	0.16	0.19	0.12
Slow Rate Recovery Glucose	**0.73**	0.07	0.05	0.47	0.14
QUICKI	-0.01	**-0.94**	-0.13	0.08	-0.16
Fasting Insulin	0.02	**0.93**	0.22	0.03	0.02
Insulinogenic Index	-0.03	**0.92**	0.23	0.02	-0.08
ISICOMP	-0.25	**-0.79**	-0.24	0.16	-0.15
Evoked Insulin/Evoked Glucose	-0.10	0.46	**0.85**	0.09	-0.04
Evoked Insulin 1	0.43	0.27	**0.85**	-0.02	0.10
1 hour Insulin	0.38	0.43	**0.80**	-0.01	0.09
Slow rate Recovery Insulin	-0.07	0.11	**0.69**	0.62	0.10
Long-term Recovery Glucose	0.44	-0.07	0.19	**0.82**	0.02
2 hour Glucose	0.59	0.07	-0.03	**-0.75**	0.13
2 hour Insulin	0.51	0.41	0.30	**-0.60**	0.01
Fasting Glucose	0.14	0.08	-0.08	0.12	**0.83**
C-Peptide	-0.01	0.07	0.17	-0.11	**0.75**
Eigenvalue	6.02	3.90	2.98	2.44	1.42
% of variance (*)	31.70	20.53	15.66	12.85	7.46
Cumulative *	31.70	52.23	67.89	80.73	88.19

Note. AUCg = Incremental Area under the Curve

greater than 1. The first factor, which explained approximately 32% of the variance, encompassed glucose indices that reflected evoked glucose levels following the glucose tolerance test. The second factor, explaining approximately 21% of the variance, encompassed indices reflecting insulin sensitivity and beta cell function, which is not surprising given the strong relationship between them (Radziuk, 2000). The third factor, which explained approximately 16% of the variance, included insulin indices that were dependent on evoked insulin levels following the glucose tolerance test. The fourth factor, which explained approximately 13% of the variance, included 2-hour glucose and insulin indices. Although these indices are likely influenced by evoked glucose and insulin, they more accurately reflect glucose absorption by the cells. Finally, the fifth factor, explained approximately 8% of the variance and encompassed fasting glucose and c-peptide. These variables are not dependent on any external challenge but likely reflect steady-state function. This factor was, therefore, termed "Basal Function".

Vascular factor clusters. A principal components factor analysis with varimax rotation on the vascular factors was conducted to determine their clustering, and thus, their groupings in the subsequent regression analyses (see Table 6 for the results). Similar to the factor analysis for the glucoregulatory indices, all data from subjects who had completed at least the first cognitive assessment were included in this analysis. These analyses revealed two factors with eigenvalues greater than 1. The first factor explained approximately 48% of the variance and encompassed total and LDL cholesterol, and total triglycerides. Given their positive relationship with cardiovascular and cerebrovascular disease, this factor was termed "Risk Factor". The second factor, which explained approximately 35% of the variance, encompassed HDL cholesterol as

Table 6
Principal Components Factor Structure of the Cardiovascular Indices (n = 127-128)

	Factors	
Indices	1-Risk Indices	2-Protective Indices
Total Cholesterol	**1.00**	-.06
LDL Cholesterol	**.89**	.18
Total Triglycerides	**.50**	.40
HDL Cholesterol	.08	**-.98**
Total cholesterol/HDL cholesterol ratio	.61	**.77**
Eigenvalue	2.41	1.75
% of variance (*)	48.26	34.90
Cumulative *	48.26	83.15

well as the total cholesterol/HDL cholesterol ratio. This factor reflects the impact of HDL cholesterol and was, thus, termed "Protective Factor".

Neuropsychological factor clusters. A principal components factor analysis with varimax rotation was also conducted on the cognitive measures to determine the clustering among these measures and their groupings for the subsequent MANOVAs (see Table 7 for the results). This analysis was dependent on the participants' first cognitive assessment data as these are unconfounded by any practice effects. It included both genders and performance under the glucose and saccharin conditions to ensure a relatively large sample and thus, minimize the probability of committing type I error. Furthermore, given that the repeated MANOVA findings (see below) demonstrated no solution effect and gender effects on only a small number of measures, the variability produced by gender is likely to be minimal compared to the variability observed between the cognitive measures. In an attempt to avoid factor clustering based on highly correlated scores derived from the same cognitive measure, only the most representative score per measure was included in the analysis. In this regard, the verbal free recall total score was used to reflect verbal free recall performance as it encompasses the primacy, middle and recency scores. For the paragraph recall performance, all three scores (both immediate recalls and the delayed recall) are highly correlated (see Table 8). Given the common use of immediate recall performance in other studies, it was included in these analyses. Specifically, immediate recall following the second presentation was used because of its stronger association with delayed recall scores. For the complex figure recall, both immediate ($X = 24.37$, $SE = .50$) and delayed recall ($X = 24.31$, $SE = .46$) performances were essentially identical, $p > .05$. Given that most neuropsychological

Table 7

Principal Components Factor Structure of the Cognitive Measures (n = 126-129)

Indices	Factors			
	1-Working Memory	2-Verbal Memory	3-Visual Function	4-Processing Speed
Digit Span B	**.81**	.08	.16	.10
Digit Span F	**.78**	.02	-.08	.15
LNS	**.69**	.07	.28	.02
MBPT	**.49**	.45	.19	-.09
Arithmetic	**.44**	.23	.43	.05
Verbal Free Recall T	-.10	**.81**	.07	.07
Order Reconstruction	.14	**.71**	.03	.12
Paragraph IR-2	.21	**.56**	-.12	.19
Figure-IR	.10	.19	**.73**	-.13
Spatial Span B	.08	-.12	**.71**	.23
Spatial Span F	.18	-.14	**.59**	.33
Digit Symbol Coding	.09	.13	.08	**.84**
Symbol Search	.07	.21	.15	**.78**
Eigenvalue	2.31	1.86	1.76	1.59
% of variance (*)	17.78	14.34	13.53	12.21
Cumulative *	17.78	32.12	45.66	57.87

Note. B = Backward; F = Forward; LNS = Letter Number Sequencing; MBPT = Modified Brown Peterson Task; T = Total; IR = Immediate Recall.

Table 8
Correlations of Paragraph Recall Performance

Paragraph Recall Measure	Immediate Recall (first presentation)	Immediate Recall (second presentation)	Delayed Recall
Immediate Recall (first presentation)	-	.60*	.63*
Immediate Recall (second presentation)		-	.81*
Delayed Recall			-

Note. * $p < .000$

studies evaluate the immediate recall data of the figures, only immediate recall scores were used to reflect visual memory performance in these analyses. Data from the copy of the complex figures and the Modified Brown Peterson task baseline and waiting conditions were excluded from all analyses because performance of participants on these measures was at ceiling (see Table 9).

The findings of this factor analysis revealed that the cognitive measures clustered into four factors (see Table 7 for results). The first factor, which explained approximately 18% of the variance, included the Digit Span forward and backward (WAIS-III), the Letter-Number Sequencing task (WAIS-III), the Modified Brown Peterson Task and the Arithmetic subtest (WAIS-III). These measures all reflect attention and working memory function (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). The second factor, which explained approximately 14% of the variance, encompassed the verbal free recall, order reconstruction and paragraph recall performance, which are all the verbal memory measures. The third factor, which also explained approximately 14% of the variance, encompassed the complex figure recall, and the Spatial Span forward and backward subtests (WMS-III). This factor appeared to reflect visuospatial function (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Finally, the fourth factor, which explained approximately 12% of the variance, included the Digit Symbol Coding and the Symbol Search subtests (WAIS-III), which reflect processing speed function (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004; Wechsler, 1997a). Although no single measure purely reflects any given cognitive function, the clustering of these factors confirm theoretically-based distinctions in neuropsychological function. In summary, the resulting factor clusters obtained from all

Table 9
Test Performance Percentiles on the Modified Brown Peterson Task (MBPT) Baseline and Waiting Conditions and the Copy of the Complex Figures (CF) (n = 129)

Percentiles	Cognitive Tests		
	MBPT* (Baseline) (x=99.84, SE = .06)	MBPT* (Waiting) (x=99.41, SE = .12)	CF** (Copy) (x=33.04, SE = .21)
25th	100	100	32.0
50th	100	100	33.5
75th	100	100	35.0

Note. * Percent Correct; ** Raw Score on 36.

three factor analyses confirmed that the measures employed in this study are indeed valid and likely represent the theoretical constructs they were designed to evaluate.

Relative Contributions of the Glucoregulatory Indices and Vascular Risk Factors to the Performance on Cognitive Function

Hierarchical linear regressions were conducted to evaluate the relative contribution of glucoregulatory indices and vascular factors to the various cognitive factors. The first model comprised of age and education to account for the contribution of demographic factors. The vascular variables that clustered together and formed the "risk factor" in the factor analysis (Total cholesterol, LDL cholesterol, and total triglycerides) were then entered. The third model included the vascular factors that had comprised the "protective factor" (HDL cholesterol and total cholesterol/HDL cholesterol ratio). This model, however, revealed multivariate multicollinearity (HDL cholesterol Tolerance = .00) thus, only the total cholesterol/HDL cholesterol ratio was evaluated in this model. The second and third models allowed for a separate examination of the potential relative contributions of the risk and protective vascular factors. The remaining two models entered comprised of the glucoregulatory indices. These were entered last to ensure that any cognitive variation associated with the glucoregulatory indices was not due to the vascular factors. More specifically, the fourth model comprised the glucoregulatory factor scores primarily associated with insulin levels and function (Beta cell funtion/insulin sensitivity, evoked insulin and basal function). The fifth model comprised the glucoregulatory factor scores primarily associated with glucose levels (evoked glucose and glucose absorption). Although most these indices are highly related and that the glucose/insulin separation is primarily arbitrary, it was of interest to

determine whether levels of glucose and/or insulin were independently associated with and can predict cognitive function. Furthermore, the insulin/glucose distinctions within each model would not significantly affect the interpretation of the results as the standardized beta weights for each variable was also determined.

The R^2 change statistic, which reflects the joint contribution of the independent variables in the model when the additional variables are added to the model, and the standardized beta weights (β), which reflects the unique contribution of each independent variable given the specific model, are presented. The regression analyses were conducted using each of the four cognitive factors as the dependent variables to determine relationships between demographic, vascular and glucoregulatory factors and general cognitive functions. These analyses revealed significant R^2 change statistics for verbal memory measures ($p < .05$) when the glucose factors were added to the regressions. Specifically, the evoked glucose factor significantly contributed to the variability in verbal memory performance (see Table 10). No other significant R^2 change statistics were observed for any other model, in all the remaining regression analyses.

Taken together, these results suggest that glucoregulatory indices, particularly indices reflecting evoked glucose, appear to be most sensitive in predicting cognitive function, particularly, memory performance. Vascular factors did not appear to significantly contribute to the variability in cognitive function in these analyses, although, not surprisingly, these were significantly associated with glucoregulatory indices (see Table 11).

Effects of Solution and Gender on the Cognitive Performance of Better, Average and Worse Regulators

Table 10

Regression Analyses Evaluating the Contribution of Demographic, Cardiovascular Risk Factors and Glucoregulatory Factors on Verbal Memory Factor Scores (n = 123)

Variable	ß	R^2 change	F change	P
Step 1		.00	.06	.94
Age	-.04			
Education	.01			
Step 2		.02	.77	.51
Age	-.03			
Education	-.01			
Total Cholesterol	.30			
Total Triglycerides	-.19			
LDL Cholesterol	-.18			
Step 3		.00	.33	.57
Age	-.03			
Education	-.01			
Total Cholesterol	.59			
Total Triglycerides	-.38			
LDL Cholesterol	-.56			
Total Cholesterol/HDL Cholesterol	.22			
Step 4		.01	.26	.85
Age	-.05			
Education	.01			
Total Cholesterol	.66			
Total Triglycerides	-.40			
LDL Cholesterol	-.61			
Cholesterol/HDL	.22			
Basal Factor	.08			
Beta-cell Function/Insulin Sensitivity Factor	-.02			
Evoked Insulin Factor	-.03			
Step 5		.06	3.75	.03
Age	-.00			
Education	-.02			
Total Cholesterol	.71			
Total Triglycerides	-.47			
LDL Cholesterol	-.75			
Cholesterol/HDL	.38			
Basal Factor	.05			
Beta-cell function/Insulin Sensitivity Factor	-.03			
Evoked Insulin Factor	-.04			
Glucose Absorption Factor	-.15			
Evoked Glucose Factor	-.22*			

Note. * $p < .05$ for standardized beta coefficients

Table 11
Correlations between Glucoregulatory Indices and Vascular Risk Factor Variables (n = 125-129)

	Vascular Risk Factors						
Glucoregulatory Indices	**Total Cholesterol**	**Total Triglycerides**	**HDL Cholesterol**	**LDL Cholesterol**	**Total Chol/HDL Chol.**	**BMI**	**Exercise**
Fasting Glucose	.08	.09	-.34****	.20*	.32****	.27**	.18*
30-Minute Glucose	.10	.18*	-.23*	.12	.28**	.14	-.02
Evoked Glucose 1	.21*	.18*	-.10	.19*	.25**	.20*	-.13
Evoked Glucose 2	.30**	.23*	.03	.20*	.21*	.42****	-.14
Long-term Recovery Glucose	-.16	.00	-.27**	-.06	.12	.03	.08
Slow Rate Recovery Glucose	-.09	-.10	.04	-.06	-.09	-.21*	.26**
1 Hour Glucose	.21*	.18*	-.10	.19*	.25**	.20*	-.13
2 Hour Glucose	.30**	.23*	.03	.20*	.21*	.14	-.14
Incremental Area under Glucose Curve	.20*	.21*	.05	.14	.22	.83***	-.17
Fasting Insulin	.29**	.32****	-.17	.25**	.35****	.48****	-.30**
QUICKI	-.25**	-.28**	.17	-.22*	-.31****	-.45****	.28**
ISICOMP	-.28**	-.24**	.14	-.26**	-.31****	-.39****	.24**
2 hour Insulin Level	.33***	.30**	-.18*	.29**	.40****	.31***	-.25**
1 hour Insulin Level	.25**	.28**	-.24**	.25**	.41****	.50****	-.18*
Evoked Insulin 1	.21*	.24**	-.23**	.22*	.38****	.44****	-.13
Slow Rate Recovery Insulin	-.08	.02	-.14	-.03	.09	.30**	.05
C-Peptide	.07	.24**	-.31****	.11	.33****	.27**	.08
Insulinogenic Index	.27****	.31****	-.13	.21*	.30**	.45****	-.31****
Evoked insulin/Evoked glucose	.15	.16	-.16	.17	.26**	.43****	-.14

Note. * $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .00001$

Correlations between glucoregulatory indices and cognitive functions. Pearson's product moment correlations (r) were conducted between all glucoregulatory indices and performance of participants on all cognitive measures to determine the glucoregulatory index most consistently associated with cognitive function. Only data from the first assessment were analyzed to limit the potential practice effects of repeated test administration on the observed relationships. Furthermore, in order to avoid potential confounds of glucose on the relationship between glucoregulatory indices and cognition, only data obtained from the saccharin condition were used for the correlations. These analyses revealed that indices reflecting insulin sensitivity were more likely to be associated with cognitive function (see Table 12 for all statistically significant correlations). More specifically, as was observed in the regression analyses findings, the indices depicting glucose changes appear more sensitive to the variability in cognitive function, particularly, the verbal memory measures. The Slow Rate Recovery Glucose (SRRG) index was associated with performance on the most number of cognitive measures, including the order reconstruction task, the immediate paragraph recalls following both the first and second presentations, the delayed paragraph recall, and the verbal free recall of words falling in the middle of the list, which are typically the most difficult to encode. Other significant correlations were observed between a measure of visual attention, the Spatial Span, and evoked glucose indices as well as between the insulinogenic index and a measure of processing speed, the Symbol Search. For the purpose of determining better, average and worse glucoregulatory groups, the extreme

Table 12
Significant Correlations between Glucoregulatory Indices and Cognitive Measures (n = 62-64)

Indices	Cognitive Measures (Pearson's Correlation Coefficient)				
Slow Rate Recovery Glucose	Order Reconstruction (-0.42)***	Paragraph IR-2 (-0.35)**	Paragraph DR (-0.33)**	Paragraph IR-1 (-0.29)*	Verbal Free Recall M (-0.26)*
Long-term Recovery Glucose	Paragraph IR-2 (-0.57)****	Paragraph IR-1 (-0.48)****	Paragraph DR (-0.46)****	Verbal Free Recall P (-0.31)*	
Slow Rate Recovery Insulin	Paragraph IR-1 (-0.30)*	Paragraph IR-2 (-0.25)*			
30-Minute Glucose	Paragraph IR-2 (-0.36)**	Spatial Span B (0.28)*			
Incremental Area under Glucose Curve	Spatial Span F (0.32)**	Order Reconstruction (-0.30)*			
1 Hour Glucose	Order Reconstruction (-0.36)**	Spatial Span F (0.26)*			
2 Hour Glucose	Spatial Span F (0.29)*	Spatial Span B (0.24)*			
C-Peptide	Paragraph IR-2 (0.25)*	Paragraph DR (0.29)*			
Insulinogenic Index	Symbol Search (-0.31)*				
Evoked Insulin 1	Paragraph IR-2 (-0.29)*				
Evoked Glucose 2	Spatial Span F (0.29)*				
Evoked Glucose 1					
Fasting Glucose					
Fasting Insulin					
1 hour Insulin Level					
2 hour Insulin Level					
QUICKI					
ISICOMP					
Evoked insulin/Evoked glucose					
Total Cholesterol					
Total Triglycerides					
HDL Cholesterol					
LDL Cholesterol					
Total Chol/HDL Chol.					
BMI					
Exercise					

Note. * $p < .05$; ** $p < .01$; *** $p < .001$; **** $p < .00001$; B = Backward; F = Forward; P = Primacy; M = Middle; IR = Immediate Recall.

quartiles of the distribution of the SRRG index were used to determine the better and worse regulatory groups. The remaining 50% of the distribution was identified as average regulators.

Demographic and biological data group differences. The better, average and worse regulatory groups were divided by gender to allow for an evaluation of the potential interactive effects of gender on glucose regulation. Outliers ($\pm$ 3 standard deviations) within each of the groups were identified for the biological and cognitive data, and are reported in Table 13. As can be observed, only few random and isolated cases were identified. The outlier values were replaced with the values reflecting $\pm$ 3 standard deviations and the resulting data are presented in Tables 14 and 15. There were no significant differences between the original and transformed means ($p > .05$), thus, these transformations were unlikely to systematically affect the findings.

Chi square analyses revealed a trend for an unequal distribution of males and females across the glucoregulatory groups, χ^2 (2, N = 119) = 5.54, p = .06. Further examination, using adjusted residuals, revealed that a greater than expected proportion of females in the better regulators group (adj. res. = 2.0). Chi square analyses also revealed an unequal proportion of biochemical analysis technique across the glucoregulatory groups χ^2 (2, N = 119) = 6.91, $p < .05$). Specifically, there is a greater than expected frequency of radioimmunoassay analysis employed than chemiluminescent analysis for insulin and c-peptide levels among the better regulator group (adj. res. = 2.6). Given that the radioimmunoassay analyses tended to yield higher insulin values and lower c-peptide

Table 13
Frequency of Outliers within the Regulator Groups

	Better Regulators		Average Regulators		Worse Regulators	
	Males (n = 11)	Females (n = 22)	Males (n = 26)	Females (n = 28)	Males (n = 20)	Females (n = 12)
Measure						
Age (years)			1+	1+		1+
Exercise (minutes/week)			1+		1+	
1 hour Glucose (mmol/L)			1+	1+		
2 hour Glucose (mmol/L)			1+			
C Peptide (pmol/L)				1+		
Fasting Insulin (pmol/L)			1+	1+		
1 hour Insulin (pmol/L)			1+	1+		
2 hour Insulin (pmol/L)		1+				
Triglycerides (mmol/L)				1+		
HDL Cholesterol (mmol/L)					1+	
Cognitive Measure						
Modified Brown Peterson Task-1				1-		
Figure-Immediate Recall-1				1-		
Order Reconstruction Task-1				1+		
Figure-Immediate Recall-2		1-				

Note. 1 = First Visit; 2 = Second Visit; + outlier above the mean; - outlier below the mean

Table 14
Demographic Data of the Better, Average and Worse Glucoregulators

	Better Regulators		Average Regulators		Worse Regulators	
	Males δ (n = 11)	Females (n = 22)	Males (n = 26)	Females (n = 28)	Males (n = 20)	Females (n = 12)
Measure	Prevalence (n)					
Radioimmunoassay analyses for insulin and c-peptide (vs chemiluminescent) δ	4	17	6	15	6	6
Measure	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)
Age (years)ϒ	20.9 (0.8)	20.4 (0.6)	20.8 (0.5)	20.9 (0.5)	20.8 (0.6)	20.7 (0.7)
Education (years)ϒ	15 (0.5)	14.7 (0.4)	14.5 (0.3)	14.6 (0.3)	14.6 (0.4)	14.5 (0.5)
BMI (kg/m^2)∞	24.6 (1.8)	27.2 (1.3)	25.2 (1.2)	22.5 (1.1)	26.9 (1.3)	31.5 (1.7)
Exercise (minutes/week)ϒ * †	304.8 (104.8)	272.0 (74.1)	613.6 (68.1)	406.0 (65.7)	346.1 (77.7)	139.8.2 (100.3)
Fasting Glucose (mmol/L)	4.8 (0.1)	4.7 (0.1)	4.9 (0.1)	4.6 (0.1)	5.0 (0.1)	4.9 (0.1)
30-minute Glucose (mmol/L)*	6.6 (0.4)	6.4 (0.3)	7.4 (0.3)	7.4 (0.3)	9.3 (0.3)	9.0 (0.4)
1 hour Glucose (mmol/L)*	4.4 (0.4)	4.7 (0.3)	5.5 (0.3)	6.1 (0.3)	7.9 (0.3)	8.3 (0.4)
2 hour Glucose (mmol/L)	5.0 (0.4)	5.3 (0.3)	4.6 (0.3)	5.3 (0.3)	5.0 (0.3)	5.6 (0.4)
C Peptide (pmol/L)	656.9 (122.9)	694.8 (88.9)	774.1 (80.0)	766.0 (77.0)	768.1 (91.1)	1021.0 (117.6)
Fasting Insulin (pmol/L)* †	81.1 (20.0)	128.8 (13.9)	70.1 (12.8)	75.0 (12.3)	93.0 (14.6)	145.2 (18.8)
1 hour Insulin (pmol/L)*	324.3 (88.0)	521.3 (62.3)	415.1 (57.3)	459.2 (55.2)	765.0 (65.3)	823.4 (84.3)
2 hour Insulin (pmol/L)* †	250.4 (81.1)	474.1 (57.4)	284.2 (52.8)	383.0 (50.8)	468.6 (60.2)	558.7 (77.7)
Cholesterol (mmol/L)	4.2 (0.2)	4.6 (0.2)	4.2 (0.2)	4.4 (0.2)	4.20 (0.2)	4.5 (0.2)
Triglycerides (mmol/L)	1.4 (0.3)	1.4 (0.2)	1.3 (0.2)	1.2 (0.2)	1.6 (0.2)	1.5 (0.2)
HDL Cholesterol (mmol/L)	1.4 (0.1)	1.4 (0.1)	1.2 (0.1)	1.6 (0.1)	1.2 (0.1)	1.4 (0.1)
LDL Cholesterol (mmol/L)	2.2 (0.2)	2.5 (0.2)	2.4 (0.1)	2.3 (0.1)	2.3 (0.2)	2.4 (0.2)
Cholesterol/HDL Cholesterol †	3.3 (0.3)	3.3 (0.2)	3.6 (0.2)	2.8 (0.2)	3.7 (0.2)	3.4 (0.3)

Note. δ= unequal distribution across groups; ϒ = measures reported by participants; † Statistical difference between males and females; * Statistical difference between regulators; ∞ Statistical Interaction: Gender X Regulation (see text for details).

Table 15
Mean (SE) Cognitive Performance of Better, Average, and Worse Regulators

	Better Regulators		Average Regulators		Worse Regulators	
	Males (n = 11)	Females (n = 22)	Males (n = 26)	Females (n = 28)	Males (n = 20)	Females (n = 12)
	Cognitive Measures-First Assessment					
Arithmetic-1	17.09 (.72)	15.05 (.52)	16.27 (.57)	14.61 (.46)	15.25 (.76)	14.75 (.80)
Digit Symbol Coding-1	89.91 (5.76)	96.14 (2.45	87.73 (2.82)	89.93 (2.08)	87.50 (2.79)	93.83 (3.33)
Modified Brown Peterson Task-1	80.61 (5.70)	80.45 (2.98)	72.56 (3.53)	81.64 (2.83)	76.17 (4.52)	73.89 (4.64)
Symbol Search-1	42.82 (2.34)	42.73 (1.46)	43.73 (1.63)	42.57 (1.11)	43.90 (1.55)	45.17 (2.02)
Digit Span Forward -1	13.00 (.52)	11.83 (.45)	11.19 (.36)	11.79 (.37)	12.25 (.44)	11.08 (.51)
Digit Span Backward-1	8.91 (.69)	8.36 (.44)	7.92 (.43)	9.18 (.37)	9.40 (.60)	8.33 (.67)
Letter-Number Sequencing-1	13.27 (.63)	12.45 (.54)	11.80 (.40)	13.11 (.54)	12.55 (.56)	11.00 (.60)
Spatial Span Forward-1	9.64 (.75)	9.59 (.31)	9.08 (.42)	9.43 (.26)	10.10 (.42)	8.75 (.52)
Spatial Span Backward-1	8.73 (.51)	8.23 (.33)	8.38 (.38)	8.11 (.34)	8.75 (.29)	7.83 (.39)
Paragraph Immediate Recall-1	85.82 (3.71)	86.36 (2.26)	79.08 (2.19)	83.86 (2.56)	78.00 (2.79)	83.67 (2.81)
Figure-Immediate Recall-1	26.23 (1.41)	24.48 (1.37)	25.08 (1.06)	26.36 (.91)	24.70 (.99)	23.88 (1.26)
Verbal Free Recall-1	39.89 (2.84)	48.01 (2.41)	40.67 (1.74)	48.04 (2.12)	40.06 (2.27)	40.00 (2.46)
Order Reconstruction Task-1	14.54 (2.11)	16.76 (1.78)	12.44 (.83)	14.43 (1.57)	14.60 (1.88)	11.33 (.73)
	Cognitive Measures-Second Assessment					
Arithmetic-2	17.09 (.60)	15.23 (.64)	15.58 (.59)	13.75 (.57)	15.10 (.78)	16.17 (.53)
Digit Symbol Coding-2	93.55 (6.53)	95.14 (2.52)	89.35 (3.23)	89.68 (1.82)	85.70 (2.99)	94.00 (4.60)
Modified Brown Peterson Task-2	80.00 (4.99)	78.94 (2.85)	78.85 (2.69)	78.69 (3.58)	79.67 (3.91)	81.39 (3.95)
Symbol Search-2	43.82 (1.53)	43.82 (1.52)	43.77 (1.64)	42.82 (1.05)	43.25 (1.32)	42.68 (3.84)
Digit Span Forward -2	12.91 (.44)	11.73 (.47)	11.23 (.48)	12.00 (.35)	11.85 (.54)	11.58 (.56)
Digit Span Backward-2	8.73 (.88)	8.59 (.57)	8.50 (.51)	8.54 (.47)	8.60 (.68)	9.08 (.60)
Letter-Number Sequencing-2	13.64 (.59)	12.73 (.56)	12.08 (.53)	12.18 (.36)	12.45 (.58)	11.75 (.69)
Spatial Span Forward-2	9.55 (.58)	9.23 (.28)	9.54 (.43)	9.57 (.36)	9.60 (.44)	9.42 (.29)
Spatial Span Backward-2	9.36 (.39)	7.77 (.49)	9.08 (.37)	8.32 (.29)	8.70 (.39)	8.17 (.27)
Paragraph Immediate Recall-2	85.45 (1.97)	86.91 (2.19)	79.38 (2.92)	87.00 (1.64)	74.60 (3.51)	83.00 (2.37)
Figure-Immediate Recall-2	26.23 (1.67)	25.56 (1.36)	24.71 (1.28)	23.89 (1.00)	27.28 (.83)	26.58 (1.49)
Verbal Free Recall-2	45.23 (3.10)	43.06 (2.37)	39.66 (1.89)	44.38 (1.73)	40.94 (2.40)	41.25 (2.96)
Order Reconstruction Task-2	18.50 (2.73)	17.59 (1.61)	11.98 (1.28)	14.15 (1.25)	12.37 (1.67)	11.08 (1.56)

Note. 1 = First Assessment; 2 = Second Assessment

values, this uneven distribution of the two biochemical analyses in the better regulator group likely confounded the differences in insulin and c-peptide levels between the groups. These potential confounds were addressed and discussed in the following sections.

In terms of the demographic factors, analyses of variances revealed no differences in age and education level between the groups ($p > .05$). Males ($X = 421.5$, $SE = 49.1$) reported exercising more per week than females ($X = 272.6$, $SE = 47.0$), $F(1, 113) = 4.81$, $p < .05$. Average regulators ($X = 509.8$, $SE = 47.3$) also reported more exercise per week than better ($X = 288.4$, $SE = 64.2$) and worse regulators ($X = 242.9$, $SE = 63.4$), $F(2, 113) = 7.12$, $p < .005$. There was no difference in reported exercise frequency between better and worse regulators, $p > .05$. Body mass index analyses revealed a significant interaction between gender and glucoregulatory group, $F(2, 113) = 4.14$, $p < .05$. Tukey post-hoc analyses revealed that female worse regulators had higher body mass indices compared to male better regulators, male average regulators, and female average regulators.

Biochemical analyses revealed no significant differences between the groups in fasting plasma glucose levels ($p > .05$) nor in two-hour post load (75g) glucose levels, however, analyses of variance revealed significant glucose level differences at 30 minutes, $F(2, 113) = 30.43$, $p < .0001$ and one hour, $F(2, 113) = 43.71$, $p < .0001$, post glucose load (see Figures 1a to 4a in Appendix G for values). As expected, Tukey post hoc analyses revealed that worse regulators had the highest glucose values compared to the average and better regulators, and that the average regulators showed higher glucose levels compared to the better regulators.

The analyses also revealed significant group differences in insulin levels. There was a difference in fasting insulin levels between regulatory groups, $F(2, 113) = 5.54$, $p < .01$. Tukey post hoc analyses revealed that average regulators had lower fasting insulin levels compared to both, better and worse regulators, however, these differences are not clinically meaningful. The analyses also revealed that the females showed higher fasting insulin levels, $F(1, 113) = 7.53$, $p < .01$, and higher 2-hour insulin levels compared to males, $F(2, 113) = 6.85$, $p < .05$. Analyses comparing one-hour post glucose insulin levels revealed a main effect of glucoregulatory group, $F(2, 113) = 16.98$, $p < .0001$. Post hoc analyses showed that worse regulators had the highest insulin levels compared to the better and average regulators. A similar pattern was observed for two-hour post-glucose insulin levels. Analyses revealed a main effect of glucoregulatory group, $F(2, 113) = 4.51$, $p < .05$, in which worse regulators showed higher 2-hour insulin levels compared to average regulators (See Figures 1b to 4b in Appendix G for insulin values). There were no significant group differences in c-peptide levels, $p > .05$.

Cardiovascular risk factors (total cholesterol, HDL cholesterol, LDL cholesterol, and Total Chol/HDL Chol ratio) were also compared across the glucoregulatory groups, however, the findings revealed no significant differences between the groups, with the exception of overall gender differences in total cholesterol/HDL ratios, $F(1, 112) = 4.19$, $p < .05$. Specifically, males showed higher ($X = 3.5$, $SE = .1$) ratios compared to females, ($X = 3.2$, $SE = .1$).

Analyses were also conducted to evaluate the effects of solution administration (glucose versus saccharin) across the glucoregulatory groups (see Figures 5 and 6 in Appendix G for glucose levels). These ANOVAs revealed significant group differences

in the glucose condition, $F(2, 113) = 3.67$, $p < .03$. Tukey post-hoc analyses revealed that worse regulators showed higher fasting glucose levels compared to average regulators. There were no differences between better and average regulators. A similar trend was also observed for the saccharin condition. Analyses also revealed that females showed lower fasting glucose levels compared to males during both, the glucose, $F(2, 113) = 11.95$, $p < .001$, and saccharin conditions, $F(2, 113) = 5.43$, $p < .02$. However, the differences do not appear to be clinically meaningful. As expected, the glucoregulatory groups showed significantly different glucose levels following glucose administration, $F(2, 113) = 8.58$, $p < .0001$, which was not observed following saccharin administration, $p > .05$. Tukey post-hoc analyses revealed that the better regulators showed lower glucose levels compared to the worse and average regulators. Although not statistically significant, the worse regulators showed higher glucose values compared to the average regulators following glucose administration. In the saccharin condition, females also showed lower 1 hour glucose levels compared to the males, $F(1, 113) = 6.53$, $p < .05$. There was no evidence of hypoglycemia (glucose level < 3 mmol/L) during either testing sessions. Indeed, glucose levels post saccharin administration were greater than 4.94 mmol/L for all groups. It is thus unlikely that hypoglycemia is a contributing factor to the reported cognitive differences.

Cognitive differences. In total, four repeated multiple analyses of variances (MANOVA) were conducted to determine the effects of glucoregulation and gender on cognitive function. As indicated above, the dependent variables used in each analysis were determined using the clustering results produced by the factor analyses. Independent between-subjects variables included glucoregulatory group (better, average

and worse regulators) and gender (male versus female). The repeated measure was the solution ingested (glucose versus saccharin).

There were no significant multivariate effects, with the exception of significant main effects of glucoregulation, Wilks' Lambda = .83, $F(6, 214) = 3.4$, $p < .005$, and gender, Wilks' Lambda = .92, $F(3, 107) = 3.3$, $p < .05$, on the verbal memory measures (verbal free recall, order reconstruction and paragraph recall performance; See Figures 7 to 9 in Appendix G). Univariate analyses revealed significant glucoregulatory effects on paragraph recall, $F(2, 109) = 4.18$, $p < .05$, and order reconstruction, $F(2, 109) = 4.78$, $p < .05$. Specifically, Tukey post-hoc analyses revealed that the better regulators ($x = 86.06$, $SE = 1.6$) showed superior performance on the paragraph recall task compared to the worse regulators ($x = 79.46$, $SE = 1.6$). The performance of average regulators ($x = 82.14$, $SE = 1.2$) did not differ between either, the better or worse regulators. On the order reconstruction task, the better regulators ($x = 16.76$, $SE = 1.1$) outperformed both, the worse ($x = 12.4$, $SE = 1.1$) and average regulators ($x = 13.29$, $SE = 0.8$). Univariate analyses also revealed a significant gender effect on paragraph recall performance, with females ($x = 85.1$; $SE = 1.2$) recalling more information than males ($x = 80.0$; $SE = 1.3$), $F(1, 109) = 8.6$, $p < .005$). There was also a trend for relative superior performance of females ($x = 44.17$; $SE = 1.2$) compared to males ($x = 41.1$; $SE = 1.2$) on the verbal free recall task, $F(1, 109) = 3.35$, $p = .07$). No gender differences were observed on the order reconstruction task, $p > .05$.

Discussion

Neuropsychological Function Associated with Glucose Regulation

The primary objective of this study was to evaluate the neuropsychological function associated with glucose regulation in young nondiabetes patients. Several statistical analyses were conducted to address this objective. Overall, regression analyses revealed that glucoregulatory factors indeed predicted cognitive performance, independent of demographic and vascular risk factors. Specifically, these findings showed that the evoked glucose factor significantly predicted verbal memory factor scores, which reflected performance on paragraph recall, word list recall, and word order recall/reconstruction. The cognitive factor scores (i.e., working memory; verbal memory; visual attention and memory; processing speed) obtained from the cluster analyses of cognitive measure reflected theoretical, clinical, and empirical distinctions in neuropsychological functions (M. D. Lezak, 1995; M. D. Lezak, Howieson, & Loring, 2004). Thus, the significant associations observed in the regression analyses suggest that glucose regulation is indeed associated with particular neuropsychological function rather than with the unique variability of a single cognitive measure. Evaluation of the significant beta weight, however, revealed a relatively weak association, at -.22, which suggest that approximately only one fifth of the changes in the standard deviation of glucoregulatory indices were associated with changes in cognitive performance.

Repeated multiple analyses of variance designed to evaluate the performance differences between participants with relatively better, worse or average glucose regulation also showed that cognitive performance was associated with glucose regulation. Specifically, better regulators showed superior performance relative to worse regulators on verbal memory measures (paragraph recall and word order recall/reconstruction), with the performance of average regulators falling in between.

When comparing the extreme quartiles of the group, effect size estimates (Cohen's *d*) of the differences between better and worse regulators were medium (.4) for both verbal memory measures. Effect size estimates for the differences between the average regulators and the other two groups on these measures, however, were somewhat smaller (.3). Thus, it appears that comparisons between the extreme glucoregulatory quartiles may be necessary to reveal stronger effects in a young healthy sample in which it is more difficult to observe variability in glucose regulation and cognitive function. Indeed, significant differences between extreme quartiles have been reported in several studies evaluating the performance of nondiabetic adults (Abbatecola et al., 2004; R. T. Donohoe & Benton, 1999; Martin & Benton, 1999). These findings also suggest that glucoregulatory effects are likely the result of significant effects within a relatively highrisk subgroup rather than a reflection of small effects across the entire sample.

Taken together, these results demonstrated that when a comprehensive assessment of cognitive function is conducted, glucoregulatory effects are most likely to be observed on measures of episodic memory. This finding supports our main hypothesis that glucose regulation is primarily associated with decrements in episodic memory function and further substantiates the literature on glucose dysregulation, including studies of type 2 diabetes (Awad, Gagnon, & Messier, 2004; Stewart & Liolitsa, 1999; Strachan, Deary, Ewing, & Frier, 1997), as well as studies of impaired glucose tolerance (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Vanhanen et al., 1997; Vanhanen et al., 1998) and of relatively poor glucose regulation in nondiabetes patients (Abbatecola et al., 2004; Allen, Gross, Aloia, & Billingsley, 1996; S. Craft, Murphy, & Wemstrom, 1994; R T Donohoe & Benton, 2000; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold,

1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; MacLullich, Deary, Starr, Walker, & Secki, 2004; C A Manning, Hall, & Gold, 1990; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997; Riby, Meikle, & Glover, 2004).

Furthermore, given that several types of verbal memory measures were evaluated in the same sample, including contextual versus noncontextual verbal measures, and that task difficulty among the verbal measures varied, these variables were examined to determine the type of memory function most sensitive to glucose regulation. Previous studies have shown that both contextual and noncontextual verbal memory measures appear to be associated with glucose regulation (S. Craft, Murphy, & Wemstrom, 1994; P. K. Elias et al., 1997; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997; Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988; Perlmuter et al., 1984; Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987; G M Reaven, Thompson, Nahum, & Haskins, 1990; C. M. Ryan & Geckle, 2000; Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; van Boxtel et al., 1998; Vanhanen et al., 1997; Vanhanen et al., 1998; Wahlin, Nilsson, & Fastbom, 2002; Worrall, Moulton, & Briffett, 1993), whereas other studies have not (Desmond, Tatemichi, Paik, & Stern, 1993; Grodstein, Chen, Wilson, & Manson, 2001; Kilander, Nyman, Boberg, & Lithell, 1997; Lowe, Tranel, Wallace, & Welty, 1994; Mattlar, Falk, Rönnemaa, & Hyyppä, 1985; Scherr et al., 1988; Vanhanen et al., 1999; Zaslavsky, Gross, Chaves, & Machado, 1995). The study demonstrates that when using the same sample, both contextual and noncontextual measures appear to be associated with

glucoregulatory effects. Similarly, it appears that the level of task difficulty (based on percent recall) is independent of glucoregulatory effects, as group differences were observed on both, the easiest (paragraph recall) and most difficult measure (word order recall/reconstruction).

The results revealed significant differences between the recall scores of the two alternate measures of paragraph recall (contextual measure), suggesting that one version is more difficult than the other. Although this would have had significant effects in a between-subjects design, it is unlikely that the difference between these two alternate measures systematically affected the results of this study because both versions were counterbalanced across the two assessment dates and across the solutions administered. Furthermore, the repeated-measures analyses revealed significant main effects of glucose regulation on paragraph recall performance, across both sessions (reflecting performance across both alternates for each subject). Given that glucoregulatory effects were observed independent of task difficulty, it is unlikely that glucose regulation interacted with the two alternate measures of paragraph recall. This is further supported by the fact that inter-test variability (between the two versions of paragraph recall) is likely smaller than between-test variability (between either version of paragraph recall and any other cognitive measure).

Taken together, these findings suggest that glucoregulatory effects appear to be primarily associated with one's ability to encode and retrieve information, independent of task difficulty and the degree of contextuality. This is also supported by the significant relationships observed between glucoregulatory indices and the primacy and middle measures (correlation analyses) of the verbal free recall task (word list learning), which

both require active encoding of information rather than short-term maintenance of the information in working memory, typically reflected by the recency recall (Baddely & Hitch, 1974). It has been well-documented that medial temporal lobe structures, including the hippocampus, are involved in the encoding and retrieval of episodic memories (Deweer, Pillon, Pochon, & Dubois, 2001; Eichenbaum & Cohen, 2001; Rosenbaum, Winocur, & Moscovitch, 2001) and that the intactness of these structures is independent of working memory function (e.g., (Nadel & Moscovitch, 1997)). Although the association between episodic memory and medial temporal lobe was initially observed in patients with temporal lobectomies, recent studies have demonstrated the association in other populations, including healthy individuals. For example, it has been demonstrated that shrinkage of the entorhinal cortex (as documented on MRI) and not the hippocampus or prefrontal cortex, over a five-year period, predicted poorer episodic memory performance in healthy adults (mean age 58 years)(Rodrigue & N., 2004). Furthermore, parahippocampal and anterior hippocampal activation (using functional magnetic resonance imaging scanning) appear to be associated with the encoding and retrieval of the initial words in a list (i.e., primacy effect), whereas perirhinal activation appears to be associated with recall of all words (Strange, Otten, Josephs, Rugg, & Dolan, 2002). More recently, it was shown that recognition of early items (primacy effect) in a word list uniquely activated the hippocampal memory system on MRI, whereas no such activation was observed with the recognition of the later items (recency effect) (Talmi, Grady, Goshen-Gottstein, & Moscovitch, 2005). These studies support the view that encoding and later retrieval of information involves distinct medial temporal lobe areas, which are different from the areas involved in the short-term storage

of information (i.e., working memory). Although, there is some inconsistency regarding the specific structures involved, glucose regulation appears to be associated with general medial temporal lobe function. This hypothesis is further substantiated by the observation that neuroelectrophysiologic activity appears to differentiate nondiabetic better and worse glucose regulators during euglycemia, with worse regulators showing smaller p300b amplitude (Knott, Messier, Mahoney, & Gagnon, 2001), a component that has been associated with hippocampal function (Patel & Azzam, 2005). Furthermore, a more recent study demonstrated a direct association between glucose regulation and medial temporal lobe function with evidence of significant correlations between memory function and hippocampal volume and measures of glucose tolerance in normal aged humans (Convit, Wolf, Tarshish, & De Leon, 2003).

Glucoregulatory effects were primarily observed on measures of verbal memory, however, there were no significant associations between glucose regulation and visual/nonverbal memory, which also requires medial temporal lobe function. Although most studies have shown glucoregulatory effects on verbal memory, there are some studies that have also shown glucoregulatory effects on visual memory tasks (S. Craft, Murphy, & Wemstrom, 1994; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Vanhanen et al., 1997). Upon examination of the frequency of verbal versus visual memory measures employed in these glucoregulatory studies, it appears that verbal memory measures were more frequently employed, approximately 1.5 (diabetes studies) to twice (nondiabetic studies) the frequency of visual/nonverbal memory measures. Thus, it is possible that this discrepancy in frequency could account for the apparent significance of verbal memory relative to the visual memory effects, particularly given

that the effects are generally small.

Gender Effects

Another important goal was to determine whether gender interacts with the performance of participants with varying levels of glucose regulation. Using the same glucoregulatory cutoffs for group formation, more females were categorized as better regulators and more males were identified as worse regulators, whereas there was no statistical difference between the number of males and females in the average regulator group. This suggests that males were more likely to show relatively worse glucose regulation in this sample of young nondiabetic adults, (which is also confirmed by the need to include a screening session in this study to selectively recruit females with relatively worse regulation). Indeed, some population studies have shown that greater incidence and/or prevelance of type 2 diagnoses in men relative to women (Bourdel-Marchasson et al., 1997; Leibson, O'Brien, Atkinson, Palumbo, & Melton, 1997), particularly for the younger age brackets (40-54 years) (Wroblewski, Gottsater, Lindgarde, Fernlund, & Sundkvist, 1998). However, some of these differences could be attributed to other factors, including differences in body mass index (Wroblewksi et al., 1998). Nevertheless, the findings from the multiple analyses of variance did not reveal any interactions between gender and glucose regulation. Thus, when males and females are categorized as better or worse glucose regulators using the *same* glucoregulatory cutoffs for each gender, the performance of males and females do not appear to differ across each level of glucose regulation. This lack of gender difference was also observed in previous studies (R J Kaplan, Greenwood, Winocur, & Wolever, 2000; Messier, Desrochers, & Gagnon, 1999; Vanhanen et al., 1997). It is also consistent with the

observation that both males and females with impaired glucose regulation or type 2 diabetes have shown cognitive decrements (Awad, Gagnon, & Messier, 2004; Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; MacLullich, Deary, Starr, Walker, & Secki, 2004; Stewart & Liolitsa, 1999; Strachan, Deary, Ewing, & Frier, 1997; Vanhanen et al., 1997; Vanhanen et al., 1998). Nevertheless, given the unequal distribution of the genders across the extreme glucoregulatory groups in this study, it is also possible that the lack of a significant interaction with gender in this study, is attributed to insufficient power to detect an interaction between gender and regulation. Additional studies are needed to confirm that males and females with similar levels of glucose regulation are also comparable in their cognitive functions.

Although no significant interaction between gender and glucoregulation was observed, this study demonstrated that females in all groups showed superior performance on paragraph recall compared to males. There was also a trend for superior performance by the females on the verbal free recall task. These findings are consistent with the known verbal memory superiority of females (Kimura, 2004). Given the higher number of females in the better regulator group and lower number of females in the worse regulator group, it is possible that glucoregulatory effects (better regulators > worse regulators) observed on the paragraph recall task and on the verbal free recall task (regression and correlation analyses) were confounded by the superior performance of females on that measure. However, the findings of this study revealed evidence of a dissociation between gender and glucose regulation on other measures. Specifically, no gender differences were observed on the order recall/reconstruction task, although glucoregulatory effects were observed on this measure. Thus, the glucoregulatory

differences observed on the paragraph recall measure (and the trend on the verbal free recall) are likely independent of gender effects, although the possibility remains that gender differences likely inflated the actual differences between glucoregulatory groups.

The Effects of Glucose Ingestion on Neuropsychological Function

Another goal of the present study was to evaluate the effects of glucose ingestion on the cognitive function of participants identified as better, average or worse glucose regulators. Glucose ingestion has shown to improve cognitive function where improvement is possible: in participants with poor glucose regulation (S. Craft, Murphy, & Wemstrom, 1994; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R. J. Kaplan, Greenwood, Winocur, & Wolever, 2001; C A Manning, Hall, & Gold, 1990; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997) in older subjects (R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Messier, Gagnon, & Knott, 1997); in participants with probable AD(S. Craft, Zallen, & Baker, 1992; C A Manning, Ragozzino, & Gold, 1993); in schizophrenia (Newcomer et al., 1999); in Down's syndrome (C. A. Manning, Honn, Stone, Jane, & Gold, 1998) and in young college students who have sustained a head injury (Pettersen & Skelton, 2000). However, despite each participant serving as his/her own control, the findings of the current study failed to support the hypothesis that glucose ingestion would differentially improve the performance of worse regulators. Indeed, no glucose effects were observed in this study. Several reasons could account for the lack of glucose effect. To begin with, it is possible that the sample the previously reported glucose effects are the result of random test-retest performance variations. Specifically, most hyperglycemic effects were observed in smaller samples (total $n < 30$), in which neuropsychological test

variability is likely significant. The current study is the first large study to employ a repeated-measures counterbalanced design to examine glucose effects, limiting such test variability and allowing for increased power to detect true hyperglycemic effects.

The lack of glucose effect could also be explained by glucoregulatory group differences between studies. As highlighted by Messier et al. (1999), hyperglycemic facilitation appears to be more readily observable in participants who show glucoregulatory indices typical of older adults. Comparisons between the regulation of the worse regulators in the present study to that of the worse regulators identified in the Messier et al. (1999) study, revealed that the worse regulators in the current study appear to regulate glucose more efficiently. Specifically, the worse regulators in the current study showed lower peak glucose (8.6 mmol/L) following ingestion of the 50g glucose solution compared to the worse regulators in the Messier et al. (1999) study (9.8 mmol/L). Indeed, when documented, hyperglycemic facilitation has been reported in subjects with peak glucose of 9.0 mmol/L or higher (J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; C A Manning, Hall, & Gold, 1990; Messier, Gagnon, & Knott, 1997).

It is also possible that the knowledge of solution administered affected participant performance during the assessments. Indeed, 57% of participants in the present study correctly identified the solution administered, suggesting that the type of lemonade solution (i.e., cool aid) used in this study combined with 4 mg of saccharin (Messier et al., 1999) was not completely effective in rendering the tastes of the glucose and saccharin solutions comparable. It is also possible that with the increased familiarity with saccharin over the years, participants have become more sensitive to and better able to

hyperglycemic facilitation. The use of a hyperglycemic clamp in these studies could help determine the specific time window during which hyperglycemic facilitation can be observed, while maintaining glucose levels stable over time and, thus, controlling for digestive and metabolic confounds.

Given that there were no performance differences between the glucose and saccharin conditions, the cognitive decrements in worse regulators cannot be attributed to hyperglycemia, which is substantiated by the fact that no participant showed glucose levels above 13.3 mmol/L in the glucose condition. It is also unlikely that hypoglycemia is a contributing factor to the reported cognitive differences. There was no evidence of hypoglycemia (all glucose levels > 4.94 mmol/L) during either testing session. Overall, no subject reported any clinical symptoms of hypo- or hyper-glycemia during the assessments.

Indices of Glucose Regulation Associated with Cognitive Function

Multiple indices of glucose regulation were examined to determine the most sensitive predictor of neuropsychological function. These included measures of insulin sensitivity as well as measures of beta cell function. The measures were derived from glucose and insulin levels obtained during a glucose tolerance test (using a 75g glucose load). Cluster analyses yielded five factors, which were used to predict cognitive performance in the regression analyses. The findings revealed that in young nondiabetic adults, indices reflecting evoked glucose levels (including glucose area under the curve; glucose levels at .5- and 1-hour post-ingestion; glucose level difference between .5- or 1-hour post-ingestion and fasting; glucose level difference between 1-hour post-ingestion and 2-hour post-ingestion) appear to best predict verbal memory performance. In order

to determine the glucoregulatory index most associated with cognitive function and for purposes of replicability, correlation analyses were conducted between all the glucoregulatory indices and performance on cognitive measures. These findings revealed that the difference between glucose levels 1 hour post-ingestion and glucose levels 2 hours post-ingestion (slow rate recovery glucose; SRRG) correlated with the most number of cognitive measures (verbal memory measures). Other significant correlations were also observed between a measure of visual attention, the Spatial Span, and evoked glucose indices as well as between the insulinogenic index and a measure of processing speed, the Symbol Search. However, given that these appear to be isolated, and that there is no evidence of convergence from the other analyses, these associations were deemed to reflect random findings, likely due to type 2 error (particularly given the number of correlation analyses conducted).

Taken together, these findings support our hypothesis that measures of evoked glucose levels in nondiabetes patients appear to be most sensitive to the variability in cognitive function, and are consistent with previous findings (Abbatecola et al., 2004; Allen, Gross, Aloia, & Billingsley, 1996; S. Craft, Murphy, & Wemstrom, 1994; R T Donohoe & Benton, 2000; J.L. Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; R J Kaplan, Greenwood, Winocur, & Wolever, 2000; MacLullich, Deary, Starr, Walker, & Secki, 2004; C A Manning, Hall, & Gold, 1990; Messier, Desrochers, & Gagnon, 1999; Messier, Gagnon, & Knott, 1997; Riby, Meikle, & Glover, 2004). Evoked or peak glucose levels in this nondiabetic group appear to best reflect the effectiveness of insulin action. Given that fasting and 2-hour glucose levels were generally within normal limits (with the exception of the 8 subjects (6%) with impaired

glucose regulation), all indices computed on the basis of these levels were likely less sensitive in estimating the effectiveness of insulin action and glycemic control in this nondiabetic sample.

This study was the first to evaluate the relationship between fasting and evoked insulin and cognitive function in young nondiabetic adults. Although, insulin levels did not appear to predict performance in this young sample, the findings revealed significant differences in evoked insulin between the glucoregulatory groups. Specifically, worse regulators had the highest insulin levels compared to the better and average regulators at one-hour post-glucose load, and showed higher insulin levels compared to the average regulators two hours post-glucose load. These findings suggest that the worse regulators in this study were also showing evidence of hyperinsulinemia. It is important to note that the insulin results in this study are likely confounded by the biochemical analysis technique (radioimmunoassay versus chemiluminescent) used across the glucoregulatory groups. Specifically, post-hoc analyses revealed an unequal distribution of biochemical analysis technique employed across the groups. Given the differences in insulin levels noted between these two analyses (with radioimmunoassay resulting in higher insulin levels), the unequal distribution of these techniques likely yielded inflated insulin values for the female better regulators. Furthermore, given that there are significantly more females in the better regulator group, it appears that the differences between the better regulators and the other two regulatory groups (average and worse) are underestimated. It is thus, likely that this underestimation resulted in lack of statistical differences between the average and better regulators' 1-hour and 2-hour insulin levels and between the better and worse regulators' 2-hour insulin levels. It is also unclear whether the

significant gender effect noted for the fasting insulin levels in this study is an artefact of the inflated female better regulators' insulin values or whether it is a true difference between the genders. Indeed, it has been demonstrated that while men and women show comparable fasting insulin, the incremental intravenous infusion of insulin appears to result in higher insulin concentrations for women compared to men, while both genders maintained comparable glucose levels (Hale, Wright, & Nattrass, 1985). This is supported by the finding that females also showed higher insulin levels in the worse regulator group in which there was no biochemical technique difference.

Although insulin levels appeared to generally follow glucose levels in each of the glucoregulatory groups, they did not appear to be as sensitive as glucose levels in predicting cognitive function. Given that the level of insulin secreted does not necessarily reflect the effectiveness of insulin in transporting glucose (Hale et al., 1985), blood glucose levels could offer a more simple measure of the effectiveness of insulin action and glycemic control.

Possible Mechanisms Underlying the Cognitive Decrements Associated with Reduced Glucose Regulation.

Despite the considerable heterogeneity in methodology among studies of glucose regulation (poor glucose regulation in nondiabetes patients, impaired glucose tolerance, type 2 diabetes), the most consistent cognitive deficit associated with reduced glucoregulation pertains to memory performance. Thus, the cognitive decrements appear to be a manifestation of a common physiological effect. As discussed above, the medial temporal lobe is likely an important locus of glucoregulatory effects. This section will provide a summary of three possible underlying mechanisms that could account for the

cognitive decrements associated with reduced glucose regulation. These include vascular dysfunction, insulin receptor distribution and function, as well as possible genetic contributions.

Impaired glucose regulation is typically associated with insulin resistance. Given that vascular pathology, including microvascular angina, increased plasminogen activator inhibitor-1, hyperuricemia, hypertension, cerebrovascular disease, and coronary heart disease, is prominent in individuals with insulin resistance (G. M. Reaven, 1993), it has been proposed that the cognitive deficits associated with impaired glucose regulation can be attributed to vascular dysfunction (Geroldi et al., 2005). Several studies evaluating the effects of vascular disease in patients with type 2 diabetes have supported this view. Specifically, Elias et al. (1997) have shown an interaction between type 2 diabetes and hypertension, resulting in greater risk of poor performance on cognitive measures. This finding is supported by a recent longitudinal study that showed that participants with both diabetes and hypertension showed the greatest cognitive decline over an 8-year period relative to patients with either diabetes or hypertension (Hassing, Hofer et al., 2004) and by a recent magnetic resonance imaging study that demonstrated cortical atrophy only in patients with both diabetes and hypertension (R. Schmidt et al., 2004). Other studies have shown an association between elevated triglyceride levels and reduced cognitive performance in type 2 diabetes patients (Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992).

One objective of the present study was to determine the contribution of vascular risk factors to the cognitive function of young nondiabetic individuals with varying levels of glucose regulation. It was hypothesized that vascular risk factors would not be

associated with cognitive decrements in this young nondiabetic sample. This hypothesis was indeed supported by the current findings as the regression analyses failed to reveal significant associations between the vascular risk factors and cognitive function and the analyses of variances failed to reveal any differences in these risk factors across the glucoregulatory groups. This was observed despite the significant correlations between the vascular risk factors and glucoregulatory function. Specifically, the most significant associations were observed between insulin indices and total triglyceride levels and the total cholesterol to HDL cholesterol ratios, with effect sizes ranging from $r^2 = .06$ to .17. Body mass index showed more significant associations with insulin indices compared to the vascular/lipid risk factors and some evoked glucose indices, with effect sizes up to $r^2 = .25$ for evoked insulin levels and up to $r^2 = .69$ for glucose area under the curve, reflecting a close to perfect association between body mass index and overall evoked glucose levels. Indeed, female worse regulators, who showed comparable BMI to male worse regulators, had higher body mass indices compared to the average regulators and male better regulators. Given this association, additional correlations were conducted between body mass index and the cognitive measures to determine whether BMI correlated with cognitive function, however, these analyses failed to demonstrate any significant relationship. In evaluating BMI levels across the groups, female better regulators showed BMI levels comparable to those observed in the worse regulator group, suggesting that BMI does not appear to consistently predict glucoregulatory status and associated cognitive function. A similar pattern was observed for exercise. Although exercise levels were primarily associated with insulin indices ($r^2 = .03$ to .10), average regulators reported exercising more per week than better and worse regulators,

suggesting that exercise in this nondiabetic sample appeared independent of glucoregulatory status as defined in this study, and independent of cognitive function (no group differences and no significant correlations were observed).

Taken together, these findings support the documented relationship between poor glucose regulation/hyperinsulinemia and vascular dysfunction (Reaven, 1993), and suggest that these relationships can be observed in a young university population. Furthermore, the current study demonstrated that although worse glucoregulators showed higher evoked insulin relative to the average and better regulators, the cognitive differences between regulators do not appear to be attributed to differences in vascular risk factors. This lack of association between vascular risk factors and cognitive function in a younger sample with varying glucose regulation appear to suggest two independent processes associated with cognitive dysfunction: The first reflects the effects of glucose regulation and the second reflects the effects of vascular dysfunction and/or cerebrovascular disease. Indeed, the findings to date have supported this view with results reflecting the independent effects of glucose regulation on cognition (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Gregg et al., 2000; Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Nilsson, Fastbom, & Wahlin, 2002; G M Reaven, Thompson, Nahum, & Haskins, 1990; Wahlin, Nilsson, & Fastbom, 2002; Worrall, Moulton, & Briffett, 1993; Zaslavsky, Gross, Chaves, & Machado, 1995), including the effects of improved glycemic control on cognition (Gradman, Laws, Thompson, & Reaven, 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993; Naor, Steingruber, Westhoff, Schottenfeld-Naor, & Gries, 1997; CM Ryan et al., 2006; Wu et al., 2003), the independent effects of vascular dysfunction on cognition (Desmond, Tatemichi, Paik, &

Stern, 1993; M. F. Elias, Wolf, D'Agostino, Cobb, & White, 1993; Kilander, Nyman, Boberg, & Lithell, 1997; Kumari, Brunner, & Fuhrer, 2000; Lopez et al., 2003; Nilsson, Fastbom, & Wahlin, 2002; Prencipe et al., 2003; Vanhanen et al., 1999; Verhaeghen, Borchelt, & Smith, 2003; Zaslavsky, Gross, Chaves, & Machado, 1995), and the interaction of glucose regulation and vascular function with the progression of disease (P. K. Elias et al., 1997; Hassing, Hofer et al., 2004; Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995; Jagusch, v. Cramon, & Hepp, 1992; R. Schmidt et al., 2004). Nevertheless, it is also possible that the measures used to evaluate vascular function are not sensitive to the early vascular changes associated with insulin dysfunction. A recent study demonstrated that increased cytokine release and associated endothelial inflammatory response (which reduces vascular nitric oxide bioavailability and increases oxidative stress), directly caused by hyperinsulinemia, was shown to account for the cognitive dysfunction observed in healthy older individuals (Fishel et al., 2005). Thus, other measures of vascular function, similar to the ones used in the Fishel et al., (2005) study, could be more effective in demonstrating the effects of vascular function and glucose regulation on the cognition of young nondiabetes patients, and remain to be investigated.

A second possible mechanism underlying the cognitive decrements associated with reduced glucoregulation involves insulin function in the brain. It has been pointed out that lipid is an important constituent of the brain because of both, myelin and the large surface-to-volume ratio of lipids in neurons (C. E. Greenwood & Young, 2001). Insulin is involved in the metabolism of lipids through the synthesis of fatty acids in the liver as well as by inhibiting the breakdown of fat in adipose tissue. It has been shown

that altering diets for as little as several weeks can affect brain lipid contents and affect cognitive performance (C.E. Greenwood, McGee, & Dyer, 1989; R. J. Kaplan & Greenwood, 1998). Furthermore, a more recent study demonstrated that a diet rich in saturated fat and refined sugar (similar to the typical Westernized diet) resulted in reduced hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning, which were attributed to a possible attenuation of neurotransmitter release (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). These findings raise the possibility that the insulin differences between the glucoregulatory groups could be a reflection of lipid brain function, particularly given the association between insulin function and vascular risk factors.

Other studies have shown that insulin and insulin receptor function, including upregulation of insulin receptor mRNA in the hippocampus and increased accumulation of insulin receptor protein in the hippocampal crude synaptic membrane fraction, are modulated by neuronal activation related to memory processing, (W. Zhao et al., 1999; W. Q. Zhao, 2001). Messier and Teutenberg (2005) explored the brain insulin resistance hypothesis as it addresses the relationship between insulin function and cognition. Several lines of investigations have supported this hypothesis (Messier & Teutenberg, 2005). To begin with, there is evidence that peripheral blood glucose regulation may change glucose uptake mechanisms in the brain. Glucose is delivered to the brain by several types of transporters, two of which that are found in the hippocampus (GLUT4 and GLUT8) are insulin responsive in the brain and are influenced by peripheral glucoregulation (Reagan et al., 2001; Vannucci et al., 1998). Studies have also shown that insulin transport into the brain is reduced in conditions of chronic peripheral

hyperinsulinemia (S. Craft, 2005), in some animal models of type 2 diabetes (Baskin et al., 1985), and in obesity where brain insulin receptors have shown reduced sensitivity to insulin (Kaiyala, Prigeon, Kahn, Woods, & Schwartz, 2000). Taken together, the studies evaluating the relationship between brain insulin function and cognition suggest that cognitive decrements associated with poor glucoregulation could be attributed to changes in brain lipid metabolism, brain insulin levels, and/or insulin receptor function.

A final factor that could account for the cognitive differences between the glucoregulatory groups is genetics. For example, it has been shown that the odds ratio for the co-existence of diabetes and Alzheimer's disease is significantly increased only for subjects with the ApoE4 allele (Lehtovirta M et al., 1995; Peila, Rodriguez, & Launer, 2002). It is possible that ApoE is also associated with cognitive decrements in nondemented individuals with impaired glucose regulation. Indeed, one study showed that men with Apo E2 allele and abnormal glucose tolerance (either impaired glucose tolerance or type 2 diabetes) had worse glycemic control as well as worse cognitive performance, as observed on a measure of executive function (Helkala et al., 2001). It remains to be determined whether this finding can be replicated in younger nondiabetic adults with poor glucoregulation and whether other genetic markers can predict cognitive dysfunction associated with impaired glucose regulation.

Summary

In summary, the results of this large repeated-measures study demonstrated that poor glucose regulation in young nondiabetic adults appears to be associated with mild cognitive decrements and do not appear to be attributed to age or education. These decrements were primarily associated with overall verbal memory function, independent

of the specific measure employed and level of difficulty. Verbal memory has been associated with medial temporal lobe function and some findings to date have attributed the glucoregulatory cognitive decrements to changes in lipid metabolism, insulin receptor distribution and function in that area, or genetic susceptibility (Apo E4 allele).

The findings demonstrated that evoked glucose levels, reflecting the effectiveness of insulin action, appear most sensitive to the cognitive decrements of a young nondiabetic sample. Given that fasting and 2-hour glucose levels were generally within normal limits, indices computed on the basis of these levels are unlikely to be sensitive to the variability in glucose regulation. Insulin and c-peptide levels also did not appear to be as sensitive as glucose levels in predicting cognitive function, which is likely attributable to the greater variability in insulin levels and that the level of insulin secretion is not necessarily associated with the rate of glucose absorption. Nevertheless, the findings demonstrated that the participants grouped as poor regulators on the basis of their evoked glucose levels, indeed showed some evidence of hyperinsulinemia. Although vascular risk factors, including body mass index, total cholesterol, triglyceride, and low-density lipoprotein levels, were associated with glucoregulatory status and hyperinsulinemia, they did not account for the cognitive variability associated with glucose regulation. Consistent with previous studies, glucoregulation effects on cognition are likely independent of vascular function. Alternatively, it is possible that more sensitive measures of vascular function (i.e., cytokine release) are needed to evaluate the possibility of a vascular etiology in young nondiabetic individuals.

An important limitation discussed in this study pertains to the unequal distribution of the females across the glucoregulatory groups, which, coupled with the superior verbal

memory performance of the females, likely confounded some of the glucoregulatory effects rendering interpretations difficult. Future studies could benefit from conducting comparisons between genders on this basis and the possibility that the genders differ in their insulin secretion, as observed previously (Hale et al., 1985) and in the current study, with females showing higher 2-hour insulin levels and possibly higher fasting insulin levels.

This study failed to support previous findings that glucose attenuates cognitive decrements. Although several factors could account for the lack of hyperglycemic facilitation, including the possibility that glucose exerts its effects shortly following ingestion and "missed" the cognitive measures most sensitive to its effects or the fact that it's a true noncontributory variable in this young sample, one method to determine whether glucose indeed exerts a facilitative effect on cognition is to employ a hyperglycemic clamp. This would ensure stable blood glucose levels over the course of the cognitive assessment and control for digestive and metabolic confounds. This method, however, could prove costly and is relatively more intrusive than the ingestion of a glucose solution. Alternatively, a careful study designed to evaluate the effects of glucose over time could also prove helpful. Although one such study has already been conducted with no evidence of time effect (Messier, Pierre, Desrochers, & Gravel, 1998), the time window evaluated was only 40 minutes. Other simpler methods have also been employed to evaluate the effects of other glucoregulatory molecules, including insulin. For example, intranasal insulin administration has shown improvement in memory and has been associated with changes in brain-evoked potentials consistent with improved

cognitive (attention/memory) function (Benedict et al., 2004; Kern, Born, Schreiber, & Fehm, 1999; Kern et al., 2001).

In conclusion, although the cognitive decrements reported in this study were mild and unlikely clinically significant, they nevertheless reflect important variation in young university students. These decrements could become more significant with age and consistently poor metabolic/vascular function over time. Indeed, approximately 6% of the sample already showed evidence of impaired glucose tolerance, which is consistent with the reports of increased prevalence of type 2 diabetes in young adults (Hoffman & Armstrong, 1996; McCance et al., 1994; Pinhas-Hamiel et al., 1996). Given that the diagnosis of type 2 diabetes has been shown to be preceded by 5 years of elevated 2-hour insulin levels (Hara, Egusa, & Yamakido, 1996), interventions aimed at increasing awareness in the youth, with the purpose of improving glucose control and optimizing cognitive functions could be necessary at this time. In addition to dietary changes, exercise has also shown to improve glycemic control (Boule, Haddad, Kenny, Wells, & Sigal, 2001; Goodyear, 1998), possibly prevent type 2 diabetes (Helmrich, Ragland, & Paffenbarger, 1994), as well as prevent cognitive decline and dementia (Larson & Wang, 2004; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Pope, Shue, & Beck, 2003), and thus, could prove an important intervention target in a young population.

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Appendix A
Summary of Studies Evaluating Cognitive Function in Type 2 Diabetes

Table A1

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.	**1990**	**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
Mogi et al.	**2004**	**69 (29.6%)**	72	10.4	**27 (47.8%)**	73	11.4
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. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.2)

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?		M	X		M		M
Atiea	10	D:15% /O:70% /I:15%	10.6		X		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	M	
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		M	D>C	D>C	M
Mattlar	7		9.3		X	X		X	X	X		
Meuter	8	D: 9%/O: 91%		11								M
Mogi		D+O: 81%; I: 19%	8		X		X			M	X	
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		sX, D>C	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	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
Wahlin		O: 39%; I: 6%			X	X					D>C	M
Worrall	8	D:24%/ O: 68%			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

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.3)

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							
Mogi		.61*				0.29	0.19			
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

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.4)

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*		
Mogi									0.58*			
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										

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.5)

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										
Mogi							0.41			
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	

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.6)

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	
Crooks et al.	**2003**	**489 (0%)**	78	18% < HS	3192 (0%)	79	13% < HS
Croxson et al.	**1995**	**33 (47%)**	80		**187 (55%)**	80	
Desmond et al.	**1993**	**29**	~71	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	
Nilsson et al.	**2002**	**36 (8%)**	85	8.2	**356 (20%)**	85	8.7
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
Verhaeghen et al.	**2003**	**385**	~85	~11			
Woo et al.	**1994**		>70		**2011 (49%)**	>70	

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.7)

Reference	D Duration (yrs)	Treatment Modality(%)	HbA1(%)	FG (mmol/L)	Neurological	Psychiatric	Depressive Sx	Medication**	Substance Abuse	BP	CVD	Cog/Educ
Population Studies												
Amato							D>C					
Crooks		D: 39%;O: 40%; I:21%					M			M	M	M
Croxson												
Desmond											X	X
Elias	0-29	I:6%								D>C; M	D>C; M	M
Grodstein	12	O: 71%/I: 38%					M		Mcg	D>C; M	X	D<C; M
Hiltunen							M				M	M
Kilander												M
Launer												M
Lindeman							D>C					D<C; M
Mangione												M
Nillson					X	X				M	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
Verhaeghen					X							
Woo												

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.8)

Reference	Overall Cog.	Cognitive Screening	Memory	Paragraph Imm	Paragraph Del	Verbal Imm	Nonverbal Imm	Nonverbal Del
Population Studies								
Amato		0.19*						
Crooks		E*						
Croxson		OR: 3.38*(1.35-8.48) <24 MMSE						
Desmond						E		
Elias				OR: 1.36(0.95-1.95)	OR: 1.49*(1.00-2.02)	OR: 0.99(0.68-1.44)		
Grodstein		0.24*		0.17	0.26			
Hiltunen		1.2 (0.6-2.4) ≤23 on MMSE						
Kilander		E				E	E	
Launer		OR:1.6 (1.2-2.2) = 22-25 MMSE						
Lindeman		0					0	
Mangione		E*						
Nilsson		E*						
Scherr		E		E	E			
Scott		E				E*	E	E
van Boxtel						E*		
Vanhanen						0.07	0.03	0.03
Verhaeghen	E*		E*					
Woo		OR: 0.92 (0.61-1.39) ≤ 7 CAPE						

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.9)

Reference	Digit Span F	Digit Span B	Spatial Span F	Spatial Span B	Mental control	Visuospatial	Digit Symbol	Processing Speed	Trails A
Population Studies									
Amato									
Crooks									
Croxson									
Desmond						OR: 3.5*(1.2-10.7)		E	
Elias	OR: 1.22(0.88-1.68)	OR: 1.08(0.77-1.52)							
Grodstein									
Hiltunen									
Kilander	E	E	E	E		E			E; E; E
Launer									
Lindeman	0.16					0.08			0.02
Mangione									
Nilsson									
Scherr	E								
Scott					E	E			
van Boxtel							E*		
Vanhanen						0			0.37*; 0.31*
Verhaeghen								E*	
Woo									

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A1 (Continued p.10)

Reference	Fluency-Letters	Fluency-Category	Abstract concept.	Reasoning	WCS	Trails B	Stroop interference	Working Memory	Long-term/Semantic	Language
Population Studies										
Amato										
Crooks										
Croxson										
Desmond			OR:10.9* (2.2-54.9)							E
Elias	OR: 1.23 (0.84-1.79)		OR:1.45 (0.98-2.14)							
Grodstein		0.23								
Hiltunen										
Kilander	E					E			E	
Launer										
Lindeman						0.09				
Mangione										
Nilsson										
Scherr										
Scott		E				E				
van Boxtel	E					E*				
Vanhanen	0.24	0.11								
Verhaeghen	E* (phonemic + cat.)	E* (phonemic + cat.)							E	
Woo										

Note. D: Diabetic subjects; C: Control subjects; CVD: Cardiovascular/cerebrovascular risk factors; Cog/Educ: Premorbid cognitive/education matching; ES: Elementary school; MS: Middle school; HS: High school; CO: College; ~: Mean age of entire sample; D: Diet; O: Oral hypoglycaemic; I: insulin; FG: Fasting Glucose of Diabetes sample; BP: Blood Pressure; **: Psychoactive Medication; Imm: Immediate; Del: Delay; F: Forward; B: Backward; WCS: Wisconsin Card Sorting; M: matched or controlled statistically; E: evaluated; X: exclusion criteria; s: serious; a: alcohol; cg: cigarette; ?: unavailable/unclear data; * statistically significant $p < .05$; +: common subjects in more than one study; SD: Statistically significant difference on at least one measure evaluated in the study; OR: Odds ratio (95% Confidence interval) for given score

Table A2

Summary of Studies Evaluating Neuropsychological Effects of Type 2 Diabetes

Reference	Overall Cog.	Cog. Screening	Verbal Memory	Nonverbal Memory	Attention	Visuospatial	Processing Speed	Executive Function
Cross-Sectional Studies								
(Assisi et al., 1996)		E		E	E,E,E,E	E		
(Atiea, Moses, & Sinclair, 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
(Cosway, Strachan, Dougall, Frier, & Deary, 2001)			E,E,E,E,E,E	E,E		E	E	E
(Dey, Misra, Desai, Mahapatra, & Padma, 1997)	E*	E			E*,E	E		E,E
(Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995)			E*,E*,E	E,E,E	E,E,E,E	E,E	E	E,E,E
(Jagusch, v. Cramon, & Hepp, 1992)			E,E*,E*	E*	E*,E		E,E*,E*	
(Lowe, Tranel, Wallace, & Welty, 1994)		E	E,E,E,E,E	E	E,E	E		E*,E*
(Mattlar, Falk, Rönnemaa, & Hyyppä, 1985)			E,E,E,E,E,E	E,E,E	E,E	E,E,E,E	E,E,E	E,E,E,E,E
(Meuter, Thomas, Gruneklee, Gries, & Lohman, 1980)	E					E	E*	
(Mogi et al., 2004)	E*		E,E				E*	E
(Mooradian, Perryman, Fitten, Kavonian, & Morley, 1988)			E*,E	E*	E,E			
(Motta et al., 1996)		E						
(Perlmuter et al., 1984)			E*		E,E*			
(Perlmuter, Tun, Sizer, McGlinchey, & Nathan, 1987)			E*		E,E		E*	E
(G M Reaven, Thompson, Nahum, & Haskins, 1990)			E*		E	E	E*,E*	E*,E*
(C. M. Ryan & Geckle, 2000)			E*,E,E,E	E,E*		E,E,E	E,E*	E,E*,E
(Sinclair, Allard, & Bayer, 1997)		E*						
(Soininen, Puranen, Helkala, Laakso, & Riekkinen, 1992)	E							
(Tun, Perlmuter, Russo, & Nathan, 1987)+							E	
(U'Ren, Riddle, Lezak, & Bennington-Davis, 1990)			E*,E*,E*		E*,E,E*,E*		E,E,E*	E
(Vanhanen et al., 1997)		E	E*,E	E*,E	E,E	E	E*,E*	E,E
(Wahlin, Nilsson, & Fastbom, 2002)			E*					E*,E
(Worrall, Moulton, & Briffett, 1993)		E*	E*					
(Zaslavsky, Gross, Chaves, & Machado, 1995)			E,E	E,E	E			
SD/ NSD	3/6	2/7	15/45	4/19	6/35	0/19	11/24	6/30

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

Table A2 (continued)

Reference	Overall Cog.	Cog. Screening	Verbal Memory	Nonverbal Memory	Attention	Visuospatial	Processing Speed	Executive Function
Population Studies								
(Amato et al., 1996)		E*						
(Croxson & Jagger, 1995)		E*						
(Crooks, Buckwalter, & Petitti, 2003)		E*						
(Desmond, Tatemichi, Paik, & Stern, 1993)			E			E*	E	E*
(P. K. Elias et al., 1997)			E,E*,E		E,E			E,E
(Grodstein, Chen, Wilson, & Manson, 2001)		E*	E,E					E
(Hiltunen, Keinanen-Kiukaanniemi, & Laara, 2001)		E						
(Kilander, Nyman, Boberg, & Lithell, 1997)		E	E	E	E,E,E,E	E	E,E,E	E,E
(Launer, 2005)		E						
(Lindeman et al., 2001)		E		E	E	E	E	E
(Mangione CM, 1993)		E*						
(Nilsson, Fastbom, & Wahlin, 2002)		E*						
(Scherr et al., 1988)		E	E,E		E			
(Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998)		E	E*	E,E	E	E		E,E
(van Boxtel et al., 1998)			E*				E*	E,E*
(Vanhanen et al., 1999)			E	E,E		E	E*,E*	E,E
(Verhaeghen, Borchelt, & Smith, 2003)	E*		E*				E	E*
(Woo, Ho., Lau, Lau, & Yeuen, 1994)		E						
SD/ NSD	1/1	6/13	4/13	0/6	0/9	1/5	3/9	2/13

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

Appendix B

Studies Evaluating the Neuropsychological Effects of Glucose Regulation in Nondiabetic Adults

Reference	Year	Subjects (n) (%Males)	Age (years ± SD)	Ed. (years)	Glucose (G) Dose	Saccharin (S) Dose	Fasting Requirement (FR)	Glucose (G) Regulation Measure
Abbatecola et al.	**2004**	Young: 218 (47%) Old: 597(46%)	Young: 43 ±13 Old: 73 ± 6	Young: 11.2 ± 4.3 Old: 6.2± 3.5			> 8 hours	HOMA
Allen et al.	**1996**	28 (21%)	73 (range : 61-87)	9.25	50 g. in 473.17 ml.	23.7 mg in 473.17 ml.	10 pm-7 am (testing)	Peak change in G relative to 100 mg/dl
Craft et al.	**1994**	Young : 27(52%) Old : 32(50%)	Young :20.8 (range : 19-28) Old :68.5 (range : 58-77)		50g. in 473.17 ml. + drops of S	2 ml. in 473.17 ml.	Overnight	60 min G-FastingG
Donohoe et al.	**2000**	46 (0%)	22 ± 2.1	Udg.	GTT :50g.		GTT :Overnight >10hrs Testing : no FR	Multiple measures were compared
Hall et al.	**1989**	Young : 12 Old : 11	Young : 20 (range : 18-23) Old : 67.4 (range : 58-77)	Young: Udg.	50 g. in 473 ml.	23.7 mg. in 473 ml.	12 am-testing	-Peak G. -Peak change in G relative to 100 mg/dl
Kaplan et al.	**2000**	20 (50%)	72.3 ± 1.4	10.6±0.3	-50 g. in 300 ml -50 g. of potatoes -50 g. of barley	23.7 mg. in 300 ml	Overnight : 10-12 hrs	-gAUC (incremental) -β cell function : 20 X fasting insulin/(fasting glucose-3.5) -Insulin resistance : fasting insulin/(22.5e$^{-\ln\text{fasting glucose}}$)
Manning et al.	**1990**	17 (29%)	73 (range : 62-84)	14	50 g. in 236.58 ml.	23.7 mg in 236.58 ml.	9 hrs	Peak G- Fasting G
MacLullich et al.	**2004**	111 (100%)	67.9 ± 1.3					Glycosylated Hemoglobin
Messier et al.	**1997**	15 (60%)	62.3 ± 6.5	15.7±3.2	50 g. in 240 ml.	50 mg in 240 ml.	12 am-testing	75 min G-FastingG
Messier et al.	**1999**	36 (50%)	21.3 ± 4.6	13	50 g. in 240 ml.	50 mg in 240 ml.	12 am-testing	60 min G-FastingG
Riby et al.	**2004**	20	68.8 ± 6	12.2 ± 2.5	25 g. in 250 ml.	38 mg in 250 ml.	Overnight	17 min G-FastingG 55 min G-FastingG

Note. Ed= Education; Udg = undergraduate; GTT = Glucose tolerance test

Table B (Continued)

Reference	Cognitive Screening/ IQ	Verbal Memory	Nonverbal Memory	Attention	Visuospatial function	Processing Speed	Frontal/ Executive Function	Language
Abbatecola et al.						-Trails A*	-Trails B* -Difference Trails B – Trails A*	
Allen et al.	-MMSE		-Figural memory 15 min. delay	-Dichotic listening*	-Figural copy -Meier Visual Test	-Trails A -Grooved Pegboard	-Verbal Fluency* -Trails B -Figural Fluency	-Boston Naming Test
Craft et al.		-Paragraph recall imm. and 10 min. delay* -Modified CVLT	-Pattern recall imm., 10 min. delay + recognition* -Implicit motor memory task	-Paced Serial Addition Test			-Verbal Fluency -Stroop	
Donohoe et al.		-Word recall imm and 15 min. delay*				-Vigilence Test* -Reaction time task		
Hall et al.		-Paired associates 24 hr delay -Paragrah recall 15 min. delay*	-Figural memory imm.*	-Digit Span				
Kaplan et al.		-Word recall imm.* -Paragraph recall imm. and 20 min. delay*		-Audiovisual attention			-Trails B*	
Manning et al.	-Ammon's Quick Test	-Buschke Selective Reminding test* -Paragraph recall 5 min. and 40 min. delay*	-Figural memory copy and imm.	-Digit Span -Letter cancellation test		-Finger Oscillation test		

Note. * significant differences associated with glucose regulation; imm= immediate; MMSE = Mini-Mental Status Examination

Table B (Continued)

Reference	Cognitive Screening/ IQ	Verbal Memory	Nonverbal Memory	Attention	Visuospatial function	Processing Speed	Frontal/ Executive Function	Language
MacLullich et al.	-National Adult Reading Test -Raven's Standard Progressive Matrices	-Rey Auditory Verbal Memory Test* -24-hr Paragraph recall*	-Visual Reproduction -Benton Visual Retention Test			-Digit Symbol Substitution Test	-Verbal Fluency	
Messier et al.	-ADAS*	-Paragraph recall imm and delay * -Paired associates		-Digit Span* -Visual Span		-Digit Symbol test -Cancellation H test*		
Messier et al.		-Word recall*						
Riby et al.	-MMSE -National Adult Reading Test	-Cued recall imm and delay-single encoding* -Cued recall imm and delay-dual encoding* -Delayed* + 1 wk recognition hits for single and dual encoding		-Mental Control -Digit Span*		-Digit Symbol Substitution Test*	-Category Fluency	

Note. * significant differences associated with glucose regulation; imm= immediate; MMSE = Mini-Mental Status Examination

Appendix C
Recruitment Script

Recruitment Script

Hello my name is Nesrine. I am a graduate student working with Dr. Claude Messier in the School of Psychology. We are interested in the area of neuroscience, more specifically, neuropsychology. We are currently conducting a large study that is funded by the Medical Research Council of Canada/Canadian Institutes of Health Research and are recruiting interested participants for the study.

For this study, we are interested in understanding how blood glucose regulation interacts with cognitive functions (e.g., memory). More specifically, we would like to determine whether drinking a glucose solution would have different effects on memory depending on how one regulates glucose. We are also interested in how other blood indices such as c-peptide, insulin, cholesterol (HDL, LDL, Total cholesterol/HDL), and triglycerides are also related to cognitive performance.

Previous research has shown that university students who did not regulate sugar very well tended to perform worse on certain memory tasks. As you may know, glucose is the primary energy source for the brain and evaluating its relationship may be useful in explaining some variability observed in memory performance. It will also help us determine the levels of glucose regulation and of other biological indices that predict poorer performance.

Participation would involve 3 visits to the university (and one screening visit*). They are done in the mornings for it's important to fast prior to the visits. Scheduling of the visits is relatively flexible.

(The screening visit: This is a half-hour visit to determine your level of glucose regulation. We are looking for individuals with a specific level of regulation and only those will be able to enroll in the study. Levels of regulation will be determined by taking three blood samples (Fasting; 15 minutes; 30 minutes), using one drop of blood with an automatic lancet following ingestion of a sugar drink. All subjects will be contacted by phone and informed about their participation in the study*.)

The first visit: This visit is mostly conducted at the University of Ottawa's health center. It will involve a nurse taking blood samples at different time intervals (1 at fasting; 3 following ingestion of a sugar drink). The blood samples will be obtained from a venous puncture. This visit will last approximately 2 hours.

The second and third visits: You will be given a flavored solution containing either glucose or saccharin. Neither the examiner nor you would know which one it will be. You will then be given a series of tests to evaluate cognitive function: You will be asked to remember digits, letters, lists of words, or one-paragraph stories as well as perform other cognitive activities such as solving arithmetic problems. Your blood glucose will be measured twice, each time obtaining one drop of blood with an automatic lancet.

At the end of your third visit, you will receive 20$. (Those who do not continue following the screening will receive $5 for that visit*.) Your participation is entirely voluntary and is independent of your course work. Those of you who are interested can write your names and phone numbers on a sign-up sheet. We will contact you to further discuss the study. Does anyone have any questions? Thank you for your attention.

*Included only during the screening procedure for poorer glucose regulation.

Appendix D
Telephone Health Screening Interview

Telephone Health Screening Interview

"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."

-Proceed with the questions on the "Telephone Interview for younger subjects" using the following notes and modifications.

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

"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

"Do you suffer from chronic hypoglycemia?"
Hypoglycemia = low blood sugar

"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?

"Do you suffer from important memory problems?"
Important = Do you have difficulty remembering important dates, events, family meetings, or gatherings etc.?

"Did you previously have a hemorrhage (intracranial)?"
CHANGE TO:
Have you previously had a hemorrhage or stroke?

"Did you suffer from a brain tumor or lesion?"

CHANGE TO:

Have you previously suffered from a brain tumor or lesion or head injury?

"Did you ever have any brain disease?"

Answers could include: Multiple sclerosis, Huntingtons, Parkinsons, Meningitis etc.

"Do you have chronic hepatitis?"

Chronic = any type of hepatitis

"How many alcoholic drinks did you take in the last week?"

"How many alcoholic drinks did you take in the last month?"

"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 alcohol questions.

"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 <u>current drug use (ie. in the past month)</u>

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 of its purpose, 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.

"Are you currently being treated for depression?"

Any type of treatment (drugs, psychotherapy etc.) results in exclusion of subject

"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.

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 _____ . Given our criteria, 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 _____ . Given our criteria, we cannot include you in this study. However, if we conduct another study at a later date in which this is not a criterion, would you like us to call you then?

Appendix E
Test Administration and Sessional Instructions

First Visit

Procedure:

Explain to the subject that they should read the consent form over carefully and sign it. Ask subject to sign both consent forms (1 copy is for them to keep and 1 copy will go in their file).

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

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. Do you have any questions?"

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

Second and Third Visits

Procedure:

"Have you had anything to eat or drink since midnight? Before we begin this morning, I'll measure your blood glucose level."

-Measure baseline blood glucose level. Record result.
-Give subject the solution to drink after you have taken their measurement.
-Record the time after they have finished drinking the sweet solution. The second glucose measurement will be taken 60 minutes after this time.
-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 (WAIS-III)

Standard Administration

Alternate Form Questions:

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? (Answer: 3)
2. Place seven disks, with approximately one-half inch between disks. Then say: How many disks are there all together? (Answer: 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? (Answer: 5)
4. If you have 3 books and give 1 away, how many do you have left? (Answer: 2)
5. How much is 6 dollars plus 3 dollars? (Answer: 9)
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? (Answer: 3)
7. Soft drinks are sold 6 cans to a package. If you want 24 cans, how many packages must you buy? (Answer: 4)
8. Chewing gum costs 25 cents per pack. How much would it cost to buy 8 packs? (Answer: 2)
9. How many hours will it take a person to walk 21 miles at the rate of 3 miles an hour? (Answer: 7)
10. If you buy 8 20-cent mints and give the clerk 5 dollars, how much change should you get back? (Answer: 3.40)
11. If you have 18 dollars and spend 9 dollars and 50 cents, how much will you have left? (Answer: 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? (Answer: 20)
13. The price of shirts is 2 for 41 dollars. What is the price of 1 dozen shirts? (Answer: 246)
14. What is the average of these numbers: 15, 5, and 10? (Answer: 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? (Answer: 1200)
16. A family drove 315 miles in 5 hours. What is their average speed in miles per hour? (Answer: 63)
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? (Answer: 68)
18. Chris has two times as much money as Robert. Chris has eighty-nine dollars. How much money does Robert have? (Answer: 44.50)

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 the chance of picking out an orange paper clip? (Answer: 1/4)
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? (Answer: 108)

Digit Symbol Coding (WAIS-III)

Standard Administration

Modified Brown Peterson Task (MBP)

Procedure:

-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.

-Set the program: Instructions will appear on the screen. Read the instructions to the subject while he or she looks at the screen.

"In this task, you will receive small amounts of information to memorize and recall. On each trial, I will say 3 consonant letters and ask you to recall them in writing as soon as you hear a tone."

-Instructions for baseline will appear. Read them to the subject while he or she looks at the screen.

"For the first part of this task, I will say 3 consonant letters and as soon as I finish, you will hear a tone. When you hear the tone, write down the letters in the same order as you heard them. There will be 14 trials. The first 4 will be practice trials."

-Put up the divider to block the screen from the subject.

-Hand the subject an MBP Block 1 recall sheet.

-The screen will read "Ready?". Ask subject if he or she is ready. Press space bar to say the letters.

-Say each letter as it is presented on the screen.

-The computer will beep after each trial and the screen will then read "Time to recall". Tell the subject *"Time to recall"*.

-This procedure repeats itself for the 3 other practice trials and the 10 experimental trials.

-Depending on the randomization, the following condition will either be the Delay

condition followed by the Interference condition or vice versa.

-For the Delay condition, instructions will appear on the screen. Read them to the subject while he or she looks at the screen. Say:

"*For the second/third part of this task, I will say 3 consonant letters and I would like you to keep the letters in memory until you hear the tone. When you hear the tone, write down the letters in the same order as you heard them. There will be 14 trials. The first 4 will be practice trials.*"

-Hand the subject an MBP Block 2 or Block 3 recall sheet depending on the randomization.

-The screen will read "Ready?". Ask subject if he or she is ready.

-Say each letter as it is presented on the screen.

-The subject will have to wait 20 seconds before the computer will beep and the screen will read "Time to recall". Tell the subject "Time to recall".

-This procedure repeats itself for the 3 other practice trials and the 10 experimental trials.

-For the Interference condition, instructions will appear on the screen. Read them to the subject while they are looking at the screen. Say:

"For the second/third part of this task, I will say 3 consonant letters and give you a 3-digit number from which I will ask you to count backwards by 3s. For example, if I gave you 133, you would say (prompt subject to count backwards). You would keep counting backwards, as quickly as you can, until you hear the tone. When you hear the tone, stop counting and try to write down the letters in the same order as you heard them. There will be 14 trials. The first 4 will be practice trials."

-Screen will read "Ready?". Ask subject if he or she is ready.

-If the subject is not counting backwards, say:
"Please count backward by 3s from the number I gave you."

-After 20 seconds, the computer will beep and the screen will read "Time to recall". Tell the subject "Time to recall".

-This procedure repeats itself for the 3 other practice trials and the 10 experimental trials.

<u>Symbol Search (WAIS-III)</u>

Standard Administration

Digit Span (WAIS-III)

Standard Administration

Spatial Span (WMS-III)

Standard Administration

Logical Memory (LM) I (WMS-III)

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 the cassette tape with the 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."

Rey (or Taylor) Complex Figure Task

Standard Administration (Meyers and Meyers, 1995)

Verbal Free Recall Task (VFR)

Word lists for the Verbal Free Recall task:

Practice	LIST 1	LIST 2	LIST 3	LIST 4
Life	City	Group	Room	Side
Public	Face	Form	Case	Saw
Thought	Family	Light	Thing	Church
Number	Door	Law	Country	Line
Water	Question	Money	College	Show
President	Office	Position	Reason	Society
War	Age	Future	Court	Force
State	Front	Voice	Wife	Board
Back	Land	Level	Control	Rate
System	Figure	Child	Art	Morning
Hand	Plan	Street	Sound	Surface
Business	Idea	Value	Call	View
	Pressure	Cut	Support	Report
	Amount	Space	Feeling	Material
	Subject	Committee	Move	Range
	Cause	Summer	Square	Meeting
	Deal	Design	Freedom	Nation
	Plane	Wish	Unit	Staff
	Season	Train	Income	Style
	Break	Equal	Cover	Bit

Procedure:

-Have the subject sit directly in front of the screen and sit next to him or her.

-Set the program: Instructions will appear on the screen. Read the instructions to the subject.

"In this task, you will be presented with lists of words to be studied. The words will be presented one at a time, but fairly quickly. You will begin with a practice list of 12 words and continue with 4 additional lists of 20 words each. After you have studied the last word of each list, I will hand you a sheet of paper and ask you to write down as many words as you can remember. You may write down the words in order you wish and you have up to two minutes to recall them. The computer will beep after one minute but you can continue for another minute. Do your best to remember as many words as you can. The practice list will give you a feel for the task."

-At the end of each list presentation, hand the subject a VFR recall sheet.

Logical Memory (LM) II - Delayed Recall and Recognition (WMS-III)

★ 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.

Recognition Trial

Standard Administration

Letter-Number Sequencing (WAIS-III)

Standard Administration. In addition, use the following instructions during the practice trials:

If the subject makes an error on 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.

Rey (or Taylor) Complex Figure Task - Delayed Recall

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

Standard Administration (Meyers and Meyers, 1995)

Order Reconstruction Task (OR)

Word Lists for the Order Reconstruction Task:

Practice	LIST 1	LIST 2
War	Table	Top
School	Tax	Peace
State	Road	Book
Way	Fire	Ground
Time	East	Hope
Man	Floor	Heart
Year	Spirit	Person
Work	Report	Island
House	River	Paper
Thought	Hall	Answer
Number	Issues	Story
Life	Stand	Effort
	Food	Fall
	Knowledge	Addition
	Letter	Size
	Purpose	Trade
	Step	Army
	Evening	Husband
	Lead	Note
	Manner	Degree

Procedure:

-Have the subject sit directly in front of the computer and sit next to him or her.

-Set the program: Instructions will appear on the screen. Read the instructions to the subject.

"In this task, you will be presented with lists of words to be studied. The words will be presented one at a time, but fairly quickly. You will begin with a practice list of 12 words and continue with 2 additional lists of 20 words each. After you have studied the last word of each list, I will hand you a sheet of paper with the words presented in alphabetical order.. Your task will be to write down the words in the same order as you saw them presented on the screen. You will have two minutes to do so. The computer will beep after one minute but you can continue for another minute. Do your best to remember the order in which the words were presented. The practice list will give you a feel for the task."

-At the end of each list presentation, hand the subject an OR recall sheet.

End of Second Visit

- Schedule the appointment for the 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
- After testing has been completed, ask *" Based on the taste, what solution do you think you had today, real sugar or artificial sugar?"*

Appendix F
Consent Forms for General Study and for Glucose Screening

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Effect of glucose on memory functions

Before you consent to participate in this study involving research, you must understand several general principles that apply to all who take part in our studies.

a) Taking part in the study is entirely voluntary

b) Personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others.

c) You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. You will still receive 20$ for your participation.

You are urged to discuss any questions you have about the study with the researcher who explains it to you.

Purpose of the study: The purpose of this study is to see if drinking a glucose (sugar) solution is helpful for memory. We also want to see if the speed at which your body assimilates glucose is linked to memory performance.

Study Plan: You will come three times at the University of Ottawa. These visits will take place on early morning and you should not take any breakfast before you arrive. It is very important that you should not eat or drink (except water) after midnight preceding each of the visits.

First visit: During the first visit, you will go to the University of Ottawa Health Center and a nurse will take 4 blood samples, one before and three after drinking a drink with sugar to measure how your body assimilates glucose. These blood samples will be obtained from a venous puncture. We will use these blood samples to measure glucose, insulin and pro-insulin levels in your blood. Blood samples will also be taken to measure total cholesterol, HDL cholesterol and total triglycerides levels. Finally the nurse will take your blood pressure. This visit will last about 2 hours.

Second and third visit:
On the second and third visit, you will be given a flavored solution to drink containing either glucose or saccharin. The examiner and yourself will not know which one it will be. You will then be given several tests to assess your concentration and your memory. These tests should last between one and two hours. These tests include measures of attentional and working memory where you have to remember digits, letters or perform arithmetic problems. A second series of tests will assess your ability to remember lists of words, series of pictures or one-paragraph stories. During these visits your blood glucose will be measured three times using a portable glucose meter. One drop of blood will be obtained using an automatic lancet (pin prick) for these tests.

Risks: You may find the fasting involved uncomfortable or tiring.

Risks for blood drawing: A little pain may be experienced.

There can be no promise or guarantee of personal benefit from participating, but your involvement may benefit others in the future.

OTHER PERTINENT INFORMATION

1. Confidentiality: When results of this study are reported, you will not be identified by name. Only Health Center staff and researchers working on the study have access to your records from the study. Once you have completed the study, any identification using your name will be removed from the records. The results of the blood tests will be sent to Dr. Jean-Charles Bruyère at the Royal Ottawa Hospital for examination: if your test results are of concern, he will contact you directly and discuss them with you. Results of blood tests can also be sent to your personal physician if you so desire. A anonymous copy of all the blood tests results will be kept in the memory laboratory.

Name and address of physician:_____

_____

_____

2. You will receive 20$ for completing this study at the end of your third visit.

3. Problems or questions: Should any problems or question about this study arise, you should contact the principal investigator, Dr. Claude Messier, at the School of Psychology, University of Ottawa, (telephone: 562-5800 ext 4562) or the co-investigators: Dr. Alain Desrochers, at the School of Psychology, University of Ottawa, (telephone: 562-5800 ext 4291), Dr. Michèle Gagnon, at the Royal Ottawa Hospital (telephone: 722-6521 ext 7030).

4. You are free to refuse to participate, to withdraw from this study at any time or refuse to answer any question without any consequence to you.

5. I wish to receive a summary of the results of this study which will be available on September 2001, at the following address: _____

_____

Please keep a copy of this document for your personal records

CONSENT FORM

Study Name: Effect of glucoregulation on cognitive functions

COMPLETE APPROPRIATE ITEM BELOW, A OR B;

A. Subject's consent.

I have read the explanation and have had the opportunity to discuss it and to ask questions. I consent to take part in this study.

Name of subject	Signature of subject	Date

B. Caregiver's Permission. (if applicable)

I have read the explanation of this study and have had the opportunity to discuss it and to ask questions. I consent to my ward's participation in this study.

Name of Guardian	Signature of Caregiver	Date

C. Statement of Investigator's Responsibility.
I have explained the nature, purpose, procedures, benefits, risks of, and alternatives to this research study. I have offered to answer any questions and have fully answered such questions. I believe that the subject, guardian, or legal representative fully understands my explanation and has freely given informed consent.

Name of Investigator	Signature of Investigator	Date

Name of Witness	Signature of Witness	Date

CONSENT TO PARTICIPATE IN BLOOD GLUCOSE SCREENING

Effect of glucose on memory functions

Before you consent to participate in the screening procedure of the Glucose Regulation and Memory Study, you must understand several general principles that apply to all who take part in this screening procedure.

a) Taking part in the screening is entirely voluntary.
b) Confidentiality: When results of this study are reported, you will not be identified by name. Once you have completed the study, any identification using your name will be removed from the records.
c) Personal benefit may not result from the screening.
d) You may withdraw from the screening and the study at any time without penalty or loss of any benefits to which you are otherwise entitled. You will still receive 5$ for your participation in the screening procedure.
e) Should any problems or questions about the study arise, you should contact
-The principal investigator, Dr. Claude Messier: 562-5800 ext. 4562;
-The co-investigator, Dr. Alain Desrochers: 562-5800 ext. 4291; or
-The co-investigator, Dr. Michele Gagnon: 722-6521 ext. 7030.
Any ethical concern regarding the ethics of this study should be directed to
-The protocol officer for ethics in research, Pavillon Tabaret, room 246, (613) 562-5800 ext. 1787.

You are urged to discuss any questions you have about the screening procedure with the researcher who explains it to you.

Purpose of the screening:
We are recruiting participants who absorb glucose at different rates. The purpose of this screening is to select a group of participants who absorb glucose at specific rates. You will help us find at which rate of glucose absorption we can detect changes in memory.

Screening Procedure:
The screening would involve drinking a 240 ml. lemon-flavored beverage containing 50 g of glucose and obtaining tw blood samples (one before the drink and one 15 minutes after the drink). Blood glucose will be measured using a portable glucose measurement instrument. One drop of blood would be obtained using a pin prick.
The blood samples will be obtained using sterile and disposable needles. The researcher will use new, disposable

gloves for each participant and the location used for the blood sampling will be disinfected following each participant.

Risks:
A little pain may be experienced from the pin prick.

Subject's Consent.
I have read the explanation and have had the opportunity to discuss it and to ask questions. I consent to take part in thi study.

_____	_____	_____
Name of Subject	Signature of Subject	Date

Statement of Investigator's Responsibility.
I have explained the nature, purpose, procedures, benefits, risks of, and alternatives to this research study. I have offered to answer any questions and have fully answered such questions. I believe the subject fully understands my explanation and has freely given informed consent.

_____	_____	_____
Name of Investigator	Signature of Investigator	Date

Appendix G
Figures for Results

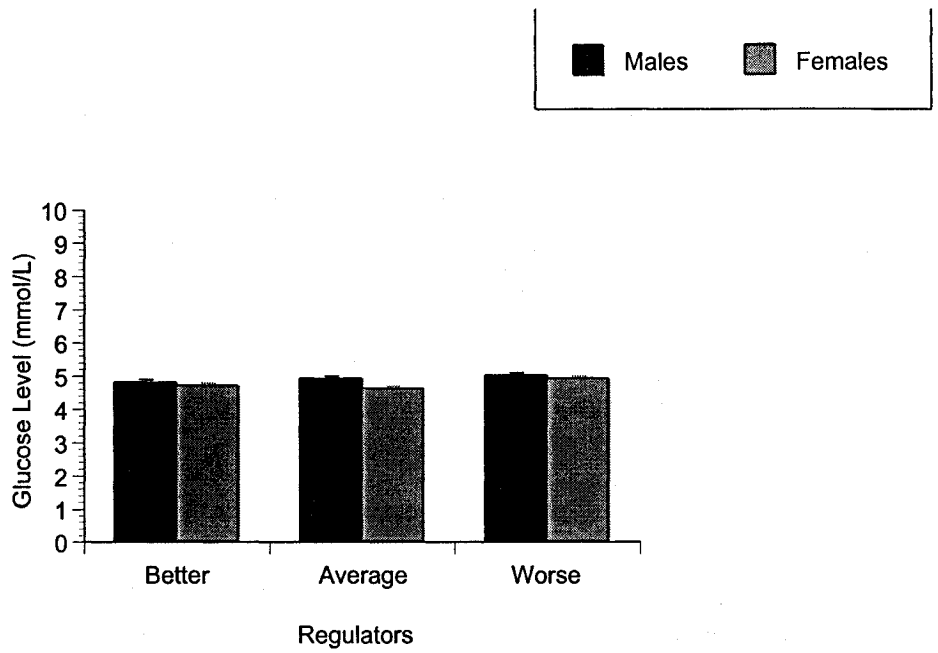

Figure 1a. Fasting glucose (mmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (*$p < .05$).

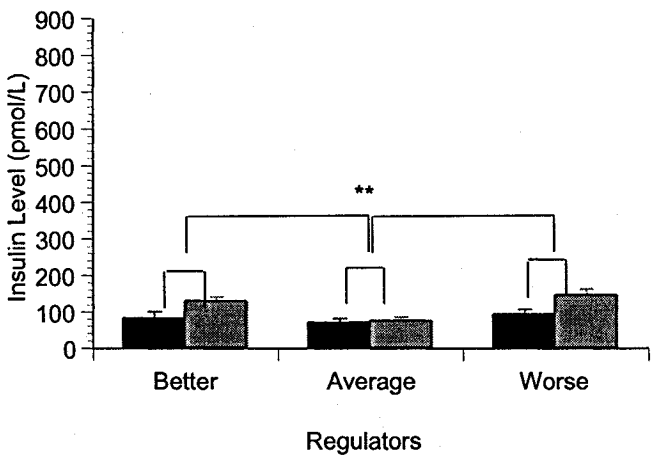

Figure 1b. Fasting insulin (pmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (**$p < .01$).

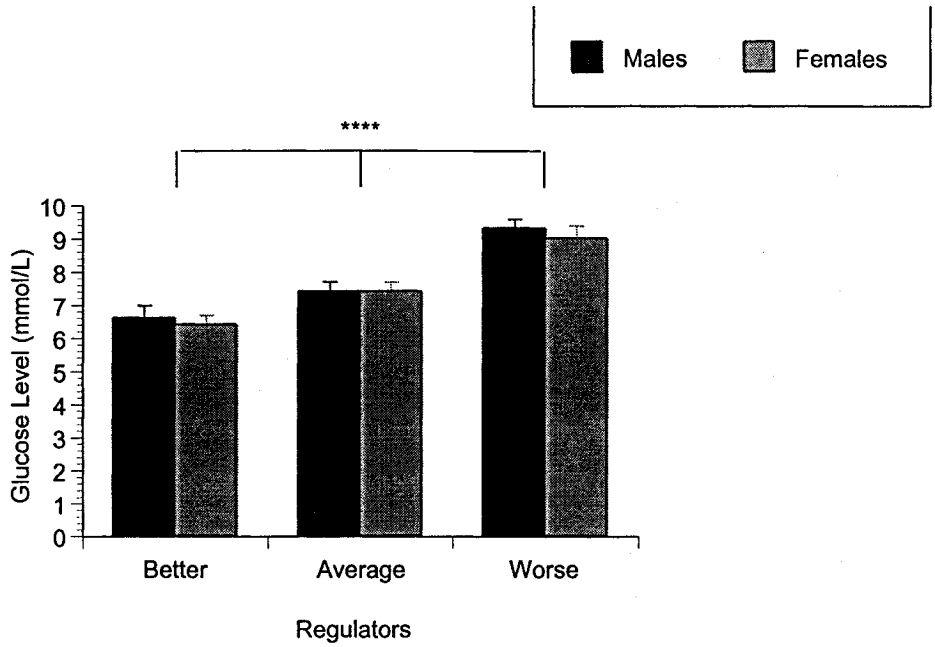

Figure 2. 30-minute glucose (mmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (****$p < .0001$).

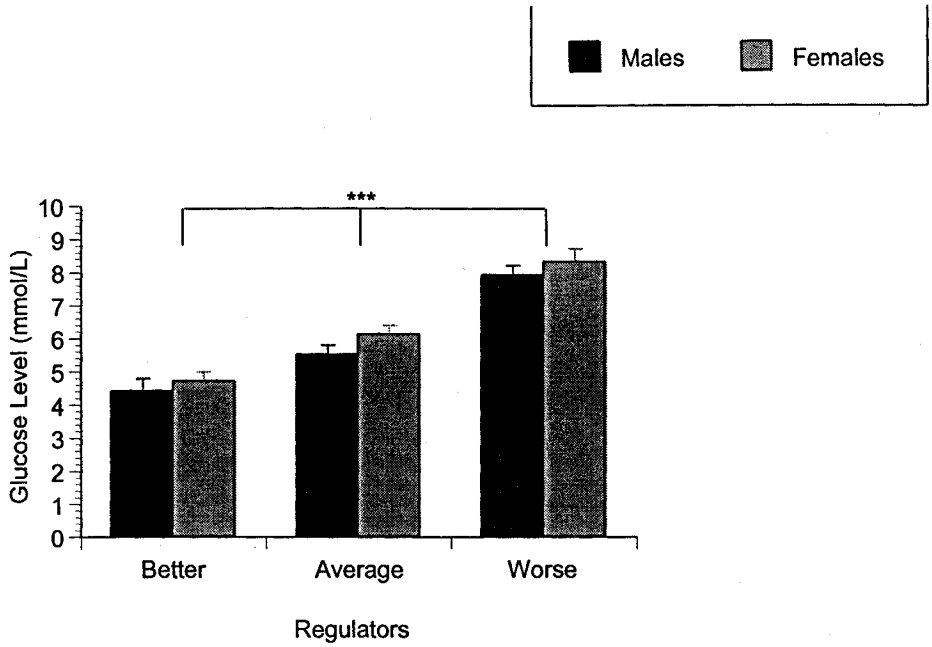

Figure 3a. 1-hour glucose (mmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (***$p < .001$).

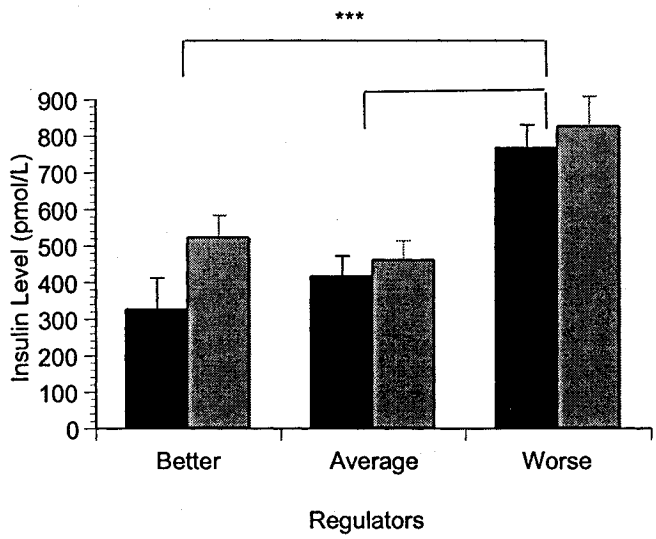

Figure 3b. 1- hour insulin (pmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (***$p < .0001$).

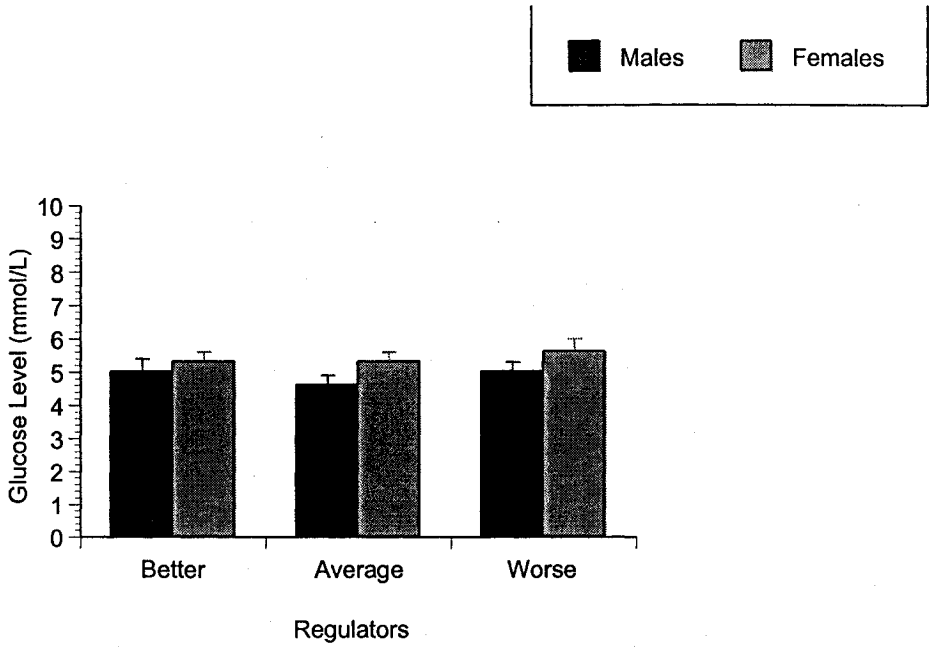

Figure 4a. 2-hour glucose (mmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (* $p < .05$).

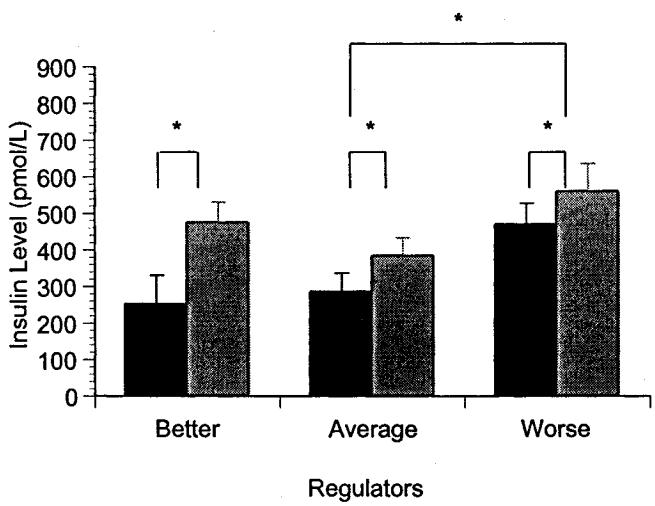

Figure 4b. 2- hour insulin (pmol/L) levels of better, average and worse regulators following ingestion of the 75g glucose solution (*$p < .05$).

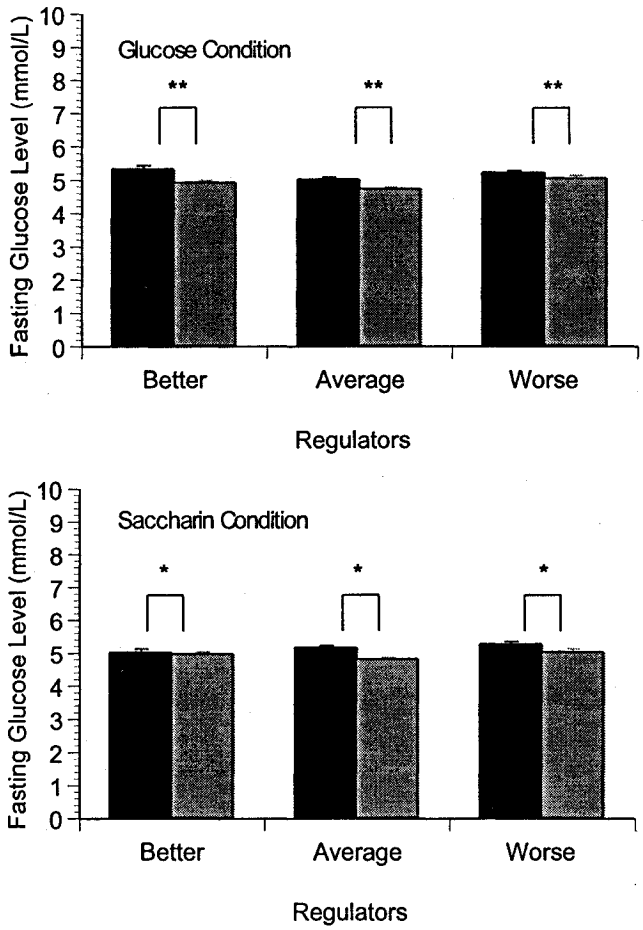

Figure 5. Fasting glucose (mmol/L) levels of better, average and worse regulators prior to ingestion of either the glucose or saccharin solutions (*p < .05; *** p < .001).

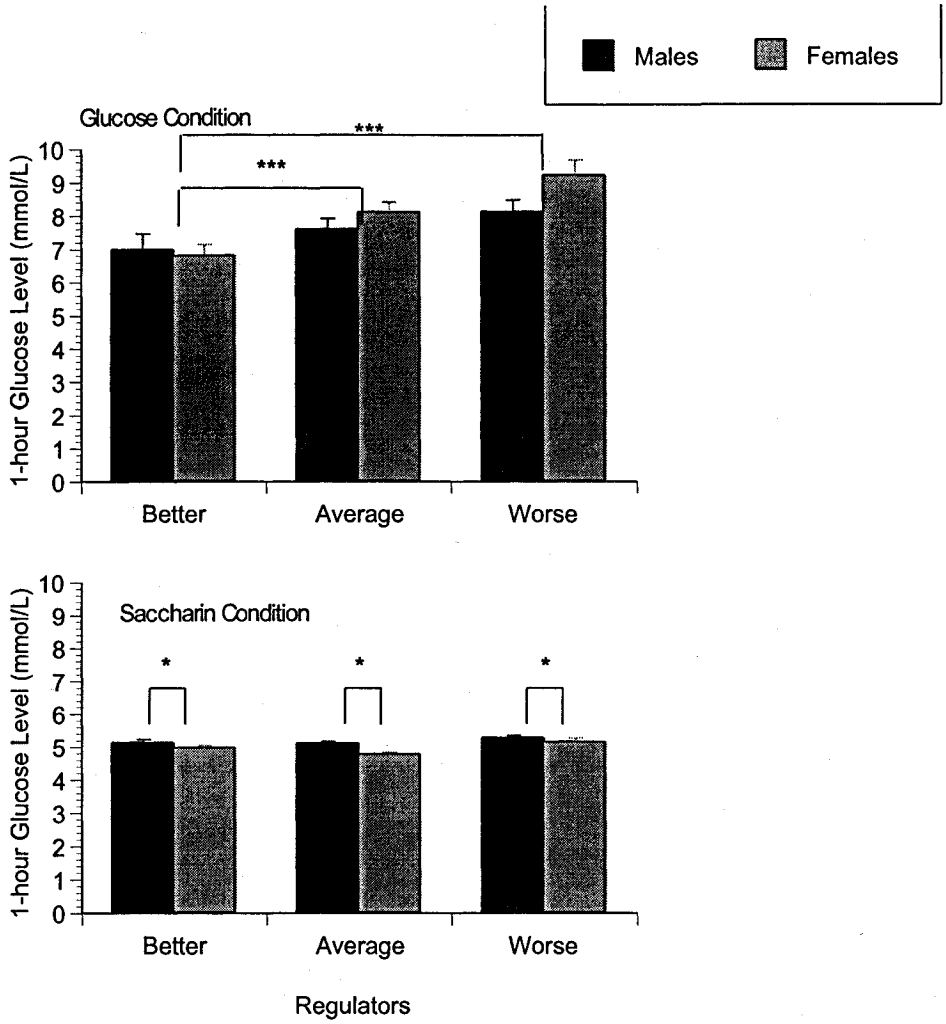

Figure 6. 1-hour glucose (mmol/L) levels of better, average and worse regulators following ingestion of the 50g glucose or saccharin solution (*p < .05; *** p < .005).

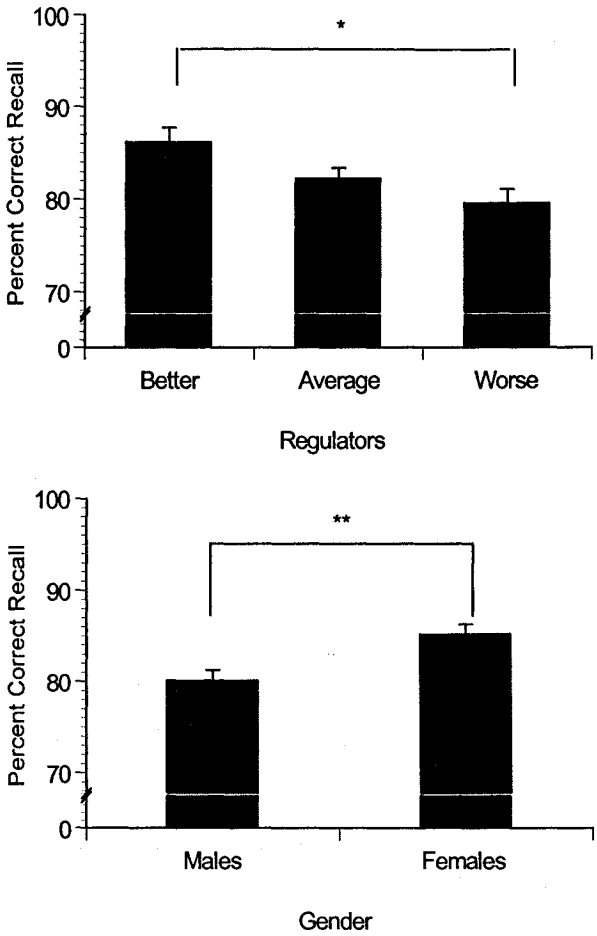

Figure 7. Mean (± SE) performance on Paragraph Recall (* $p < .05$; ** $p < .01$)

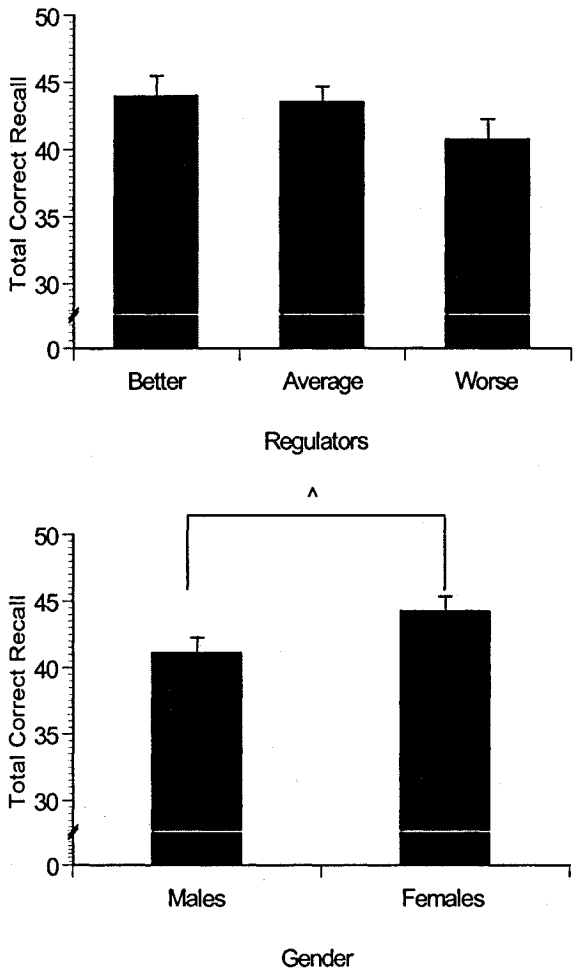

Figure 8. Mean (± SE) Performance on the Verbal Free Recall Task (^ p = .075)

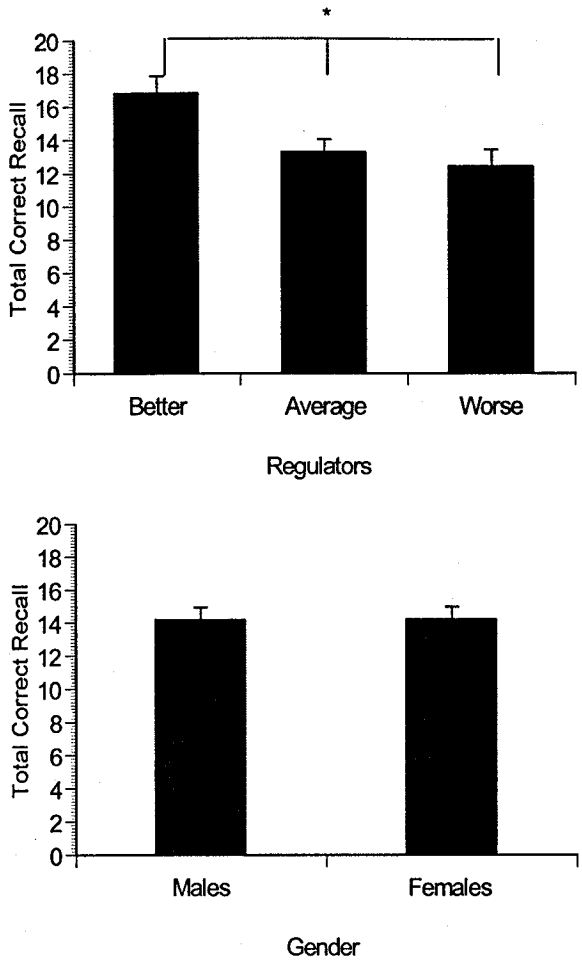

Figure 9. Mean (± SE) performance on the Order Reconstruction Task (* $p < .05$)