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Glucose dosage, dual tasks and glucoregulation as contributing factors to the glucose facilitation effect on older adults' cognitive performance

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Abstract

Animal studies have shown that there is a dose-response impact of glucose on memory but very few studies in humans have used several doses of glucose adjusted to body weight to determine whether there is more than one optimal dose. This study explored further the effect of ingested glucose on cognition in older adults by examining the impact of three doses of glucose (300 mg/kg, 650 mg/kg and 1 g/kg) on performance on neuropsychological tasks, including cognitive measures involving a concomitant or interference task. Another goal of this study was to investigate whether glucoregulation will mediate the impact of glucose on cognitive performance and if age will interact with this effect. A total of 103 older adults (mean age = 68.22) were tested twice, once after glucose ingestion and once after saccharin. Participants were categorized as younger (60-67) and older (68-85) and as better or worse glucoregulators. A doubly-multivariate analysis was conducted on 19 cognitive measures and only showed an overall significant effect of age. Some results suggest a small but not significant overall general decrease in performance on many tasks in people with worse glucoregulation. A number of methodological issues such as age and the generally high level of functioning of the participants may have reduced the ability of the present study to observe cognitive deficits or improvements.

Introduction

Glucose is utilized by the brain for energy and is transported to the brain via the blood-brain barrier (Qutub & Hunt, 2005). Research has established that glucose can improve memory in both animals and humans (see reviews by Benton, 2001; P. E. Gold, 1995, 2005; Greenwood, 2003; Korol & Gold, 1998; Messier, 2004). In rodents, glucose has been shown to improve performance on a variety of tasks including active avoidance responding when glucose was administered following passive avoidance training (Rodriguez, Horne, Mondragon, & Phelps, 1994), increase the preference for novel stimulus (Hughes, 2006), enhance spontaneous alternations in a plus-maze (McNay, Fries, & Gold, 2000), enhance performance on a working memory task (Means & Fernandez, 1992) and increase memory for reward reduction (Salinas & Gold, 2005). In humans, the improving effect of glucose has mostly been observed on tasks assessing verbal declarative memory (P. E. Gold, 1995; Messier & Gagnon, 1996), with verbal episodic memory measures being the most utilized in research on glucose and memory. A meta-analysis of studies that examined the enhancement of cognition following glucose ingestion found a general moderate effect size of glucose on cognition ($d = 0.56$) (Riby, 2004). However, the effect sizes varied greatly across cognitive domains with verbal episodic memory having the highest effect size ($d = 0.91$), working memory and semantic retrieval in the medium range ($d = 0.49$ and $d = 0.73$ respectively), visuospatial tasks, executive functioning and visuospatial episodic memory having small effect sizes ($d = 0.$ $d = 0.20$, $d = 0.24$ and $d = 0.33$ respectively) and little or no effect on measures of implicit memory, verbal intellectual ability, motor functioning and attention.

The glucose facilitation effect on cognition has been observed in adults with schizophrenia (Fucetola, Newcomer, Craft, & Melson, 1999; Newcomer et al., 1999; Stone, Seidman, Wojcik, & Green, 2003), Down's syndrome (Manning, Honn, Stone, Jane, & Gold, 1998), very mild to mild dementia of the Alzheimer's type (Craft et al., 1993; Craft et al., 1996; Craft, Zallen, & Baker, 1992) and moderate to severe dementia of the Alzheimer's type (Manning, Ragozzino, & Gold, 1993), healthy younger adults (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002; Benton, Owens, & Parker, 1994; Craft, Murphy, & Wemstrom, 1994; Donohoe & Benton, 1999; Foster, Lidder, & Sunram, 1998; Hall, Gonder-Frederick, Chewning, Silveira, & Gold, 1989; Kennedy & Scholey, 2000; Martin & Benton, 1999; Meikle, Riby, & Stollery, 2004; Messier, Desrochers, & Gagnon, 1999; Messier, Pierre, Desrochers, & Gravel, 1998; Metzger, 2000; Metzger & Flint, 2003; Owens & Benton, 1994; Parker & Benton, 1995; Riby et al., 2006; Scholey & Fowles, 2002; Scholey, Harper, & Kennedy, 2001; Scholey, Sunram-Lea, Greer, Elliott, & Kennedy, 2009; Sunram-Lea, Dewhurst, & Foster, 2008; Sunram-Lea, Foster, Durlach, & Perez, 2001, 2002a, 2002b, 2004), healthy middle-aged adults (Meikle et al., 2004) as well as healthy older adults (Allen, Gross, Aloia, & Billingsley, 1996; Craft et al., 1994; Gonder-Frederick et al., 1987; Hall et al., 1989; Manning, Stone, Korol, & Gold, 1998; Messier, Gagnon, & Knott, 1997; Parsons & Gold, 1992; Riby et al., 2006; Riby, Meikle, & Glover, 2004).

Mechanisms underlying glucose facilitation

Studies conducted in animals have elucidated the mechanisms that might underlie hyperglycemic enhancement. Several central mechanisms have been proposed. Research has indicated that glucose may enhance memory by increasing acetylcholine synthesis and release (Messier & Gagnon, 1996, 2000). More specifically, rats receiving an intraperitoneal injection of scopolamine combined with a subcutaneous injection of glucose had significantly increased levels of acetylcholine from the hippocampus compared to rats injected with scopolamine and saline (Durkin, Messier, de Boer, & Westerink, 1992).

Furthermore, administration of glucose and morphine in the medial septum not only increased spontaneous alternation in a Y-maze compared to performance in the morphine condition but the combination of glucose with morphine blocked the decline in acetylcholine release that is observed following morphine injection (Ragozzino & Gold, 1995). An increase in acetylcholine release in the hippocampus was observed in rats during spontaneous alternation testing in a four-arm cross maze but not during the resting condition suggesting that glucose (administered through an intraperitoneal injection) has an impact on acetylcholine release only when there is a demand placed on cholinergic neurons (Ragozzino, Unick, & Gold, 1996). Similarly, glucose injection in the hippocampus resulted in increased acetylcholine release and spontaneous alternations during testing in a four-arm cross maze (Ragozzino, Pal, Unick, Stefani, & Gold, 1998). However, no significant increase in acetylcholine release was observed in the resting condition, again supporting the premise that cholinergic demand is a mediating factor in acetylcholine release following glucose. Finally, glucose has also been shown to increase the amount of extracellular acetylcholine in the hippocampus of rats that had received infusions of a GABA agonist (muscimol) in the medial septum although no such increase was observed in rats given vehicle, suggesting that glucose increases acetylcholine only when there is a demand (Degroot, Kornecook, Quirion, DeBow, & Parent, 2003).

Another mechanism that has been proposed in research is the regulation by glucose of ATP-dependent potassium channels (Jafari, Zarrindast, & Djahanguiri, 2004; Rashidy-Pour, 2001). When mice were given morphine before learning a passive avoidance task, subsequent testing (24-hour delay) showed impaired recall (Jafari et al., 2004). However, when glucose and morphine were administered before recall, there was a significant enhancement of memory, above what was observed when only morphine was administered.

Glucose injection without morphine did not have an impact on recall. Furthermore, the glucose facilitation effect followed an inverted-U dose-response curve, with 100 mg/kg of glucose administered concurrently with morphine having a significant impact whereas glucose doses of 50 and 200 mg/kg failed to reach significance. The authors indicated that there are three possible mechanisms by which glucose enhances recall, including acting on cholinergic neurons by increasing acetylcholine synthesis, acting on opioidergic neurons by reversing the impact of opioid drugs or by regulating ATP-dependent potassium channels. A study conducted by Rashidy-Pour (2001) investigated the hypothesis that glucose enhances memory by modulating ATP-dependent potassium channels. Rats received an injection of either minoxidil (opens ATP-dependent potassium channels) or glibenclamide (closes ATP-dependent potassium channels) before being trained in an inhibitory avoidance task and then an injection of glucose after training. Retention after a delay of two days was significantly better in the vehicle and glucose condition compared to the minoxidil and glucose condition. The reverse was true for glibenclamide, with enhanced retention in the glibenclamide and glucose condition compared to the vehicle and glucose condition, and memory being facilitated in the latter condition compared to the vehicle and saline combination. However, minoxidil and glibenclamide alone had no impact on retention. Therefore, the interaction between glucose and these ATP-dependent potassium channel modulators supports the regulation by glucose of ATP-dependent potassium channels as the mechanism underlying the glucose facilitation effect on memory.

Studies in animals have also shown that the amount of extracellular glucose in the hippocampus is decreased during a cognitive task but that glucose can compensate for this decrease (McNay et al., 2000; McNay & Gold, 2001). Furthermore, the hippocampal extracellular glucose levels were also more markedly decreased in older rats which could result in cognitive impairments associated with age (McNay & Gold, 2001). Glucose administered with morphine in the septum reversed the decrease in spontaneous alternation in a four-arm maze that was observed following morphine alone (McNay, Canal, Sherwin, & Gold, 2006). Interestingly, extracellular glucose levels in the hippocampus were not decreased during behavioural testing in the morphine condition. However, the combination of glucose and morphine resulted in a decline in hippocampal extracellular glucose levels. Findings from these studies suggest that there is a decrease in extracellular glucose levels in the hippocampus during behavioural testing, indicating that there is a demand for glucose and that the provision of glucose can halt this decline.

Peripheral mechanisms have also been proposed. Both fructose, which does not cross the blood-brain barrier, and glucose have demonstrated to improve performance on an active avoidance task (Rodriguez et al., 1994). Another study used L-glucose to investigate whether a peripheral mechanism underlies hyperglycemic enhancement since L-glucose does not cross the blood-brain barrier (Lawson, Homewood, & Taylor, 2002). Performance of mice on the Morris water maze was significantly enhanced by L-glucose and this effect was cancelled when glucose was combined with peripheral cholinergic antagonists. Similarly, another study observed increased spontaneous alternation performance on a four-arm plus maze when rats either received D-glucose or L-glucose compared to controls (Talley, Clayborn, Jewel, McCarty, & Gold, 2002). Interestingly, in rats that had undergone a vagatomy, spontaneous alternation performance was still enhanced following D-glucose but not after L-glucose. These results suggest that D-glucose acts centrally whereas L-glucose acts peripherally by altering vagal afferents.

Insulin has also been proposed to account for glucose modulation of memory since several studies have demonstrated improvements in memory in Alzheimer's patients when insulin levels were increased (Craft et al., 2003; Craft, Asthana, Newcomer et al., 1999; Craft et al., 2000; Craft, Asthana, Schellenberg et al., 1999; Craft et al., 1996), suggesting that insulin was associated with memory facilitation. However, since blood glucose levels were maintained at baseline levels, it is difficult to separate the effects of insulin and glucose. Also, two of these studies (Craft et al., 2000; Craft, Asthana, Schellenberg et al., 1999) demonstrated that memory facilitation following hyperinsulinemia is only observed in Alzheimer's patients without the ApoE4, a known risk factor for Alzheimer's disease. Furthermore, a more recent study examined the impact of different doses of insulin and showed that improvements were observed at lower doses for Alzheimer's patients with ApoE4 and at higher doses for Alzheimer's patients without the ApoE4 (Craft et al., 2003), indicating that ApoE genotype interacts with the effects of insulin on cognition.

Dose of glucose

Animal studies have illustrated that there is a dose-response impact of glucose on memory (see reviews by P. E. Gold, 1995; McNay & Gold, 2001, 2002; Messier, 2004). An inverted U-shaped dose-response curve has generally been described in the literature. For instance, rats tested in a four-arm maze made significantly more spontaneous alternations, defined as entering each of the four arms within a set of five entries, following 250 mg/kg of glucose whereas doses of 100 mg/kg and 1000 mg/kg did not significantly enhance memory (Ragozzino et al., 1996). Furthermore, 100 mg/kg of glucose has been shown to improve performance of mice on a two-choice win-stay task (M-shaped maze) measuring working memory whereas 50 mg/kg had no effect and 250 mg/kg improved performance but to a lesser extent than 100 mg/kg (Means & Fernandez, 1992). Interestingly, mice that initially received morphine before training and were tested 24 hours later following the administration of glucose combined with morphine demonstrated better memory performance with 100 mg/kg of glucose whereas 50 mg/kg and 200 mg/kg had no effect (Jafari et al., 2004). However, a study comparing the impact of six doses of glucose on learning of an active avoidance response showed that 350 mg/kg significantly improved performance while 3.2 mg/kg had no effect and doses of 10 mg/kg, 32 mg/kg, 100 mg/kg and 2000 mg/kg resulted in impaired performance (Rodriguez et al., 1994). Studies in humans have demonstrated that doses of 25 g (Foster et al., 1998; Kennedy & Scholey, 2000; Meikle et al., 2004; Meikle, Riby, & Stollery, 2005; Parsons & Gold, 1992; Riby et al., 2006; Scholey & Fowles, 2002; Scholey et al., 2001; Scholey et al., 2009; Sunram-Lea et al., 2008; Sunram-Lea et al., 2001, 2002a, 2002b, 2004), 50 g (Allen et al., 1996; Awad et al., 2002; Craft et al., 1994; Donohoe & Benton, 1999; Hall et al., 1989; Kaplan, Greenwood, Winocur, & Wolever, 2000; Manning, Stone et al., 1998; Martin & Benton, 1999; Meikle et al., 2004; Messier et al., 1999; Messier et al., 1997; Messier, Tsiakas, Gagnon, Desrochers, & Awad, 2003; Metzger, 2000; Metzger & Flint, 2003) and 75 g (Manning et al., 1993) improved cognitive functioning, particularly memory. However, very few studies in humans have used more than one dose of glucose to determine whether there is more than one optimal dose.

A study comparing six doses of glucose (10, 100, 300, 500, 800, 1000 mg/kg) adjusted to body weight in younger female adults (mean age = 21.3) showed that 300 mg/kg enhanced memory for the first five words on a list of 20 words, designated as the primacy effect (Messier et al., 1998). Another study examined the impact of various doses of glucose (10, 100 and 500 mg/kg, or 50 g) on a task assessing attention in younger adults (mean age = 19.49) and found that none of these doses significantly improved attention (Flint & Turek, 2003). Furthermore, participants receiving a solution containing 100 mg/kg of glucose made significantly more errors (endorsing the non-target stimulus) compared to participants in the saccharin condition. However, as the authors acknowledged, a limitation of this study was the use of a between-subjects design. Finally, a study conducted in younger male adults (mean age = 21.0) compared the effects of two doses of glucose not adjusted to body weight (30 g and 100 g) on memory (Azari, 1991). None of the two doses significantly enhanced immediate free recall and recognition of a list of 40 words. Since only two absolute doses of glucose were used and glucose facilitation effect is thought to follow a dose-response curve, the lack of a significant impact of glucose on memory in this study could possibly be due to the doses utilized. One study compared three doses of glucose (10 g, 25 g and 50 g) in older adults (mean age = 67.6) and found that the most effective dose was 25 g, thus following an inverted-U dose-response curve (Parsons & Gold, 1992). This dose significantly improved performance of participants on a task of verbal memory (story recall after 5 and 40 minute delays) compared to performance following ingestion of saccharin solution. However, the doses used were not adjusted according to body weight. A meta-analysis of studies on the enhancing effect of glucose on cognition found a higher effect size when a dose of 25 g was used ($d = 1.24$ for younger adults; $d = 0.79$ for older adults) than when a dose over 25 g was used ($d = 0.18$ for younger adults; $d = 0.20$ for older adults) (Riby, 2004). According to a recent review, lower doses of glucose are generally more effective in younger adults and higher doses are more effective in older adults (Messier, 2004). Hence, few studies have compared doses of glucose adjusted to body weight in humans, particularly in older adults, and examined the impact of these doses on tests assessing a variety of cognitive domains.

Task domain

Research has examined whether the enhancement produced by glucose is specific to the task domain. Overall, research has shown that glucose improves verbal declarative memory (see reviews by P. E. Gold, 1995; Messier & Gagnon, 1996; Riby, 2004). A meta-analysis of studies on the cognitive enhancing effect of glucose indicated that, when examining the impact of glucose on episodic and semantic memory, glucose significantly increased episodic memory for both younger and older adults but generally failed to improve semantic memory (Riby et al., 2006). Although glucose is generally administered before cognitive testing, several studies have also demonstrated the memory facilitation effect of glucose when administered after learning in both younger and older adults (Manning, Parsons, & Gold, 1992; Sunram-Lea et al., 2002a) or before recall following a 24-hour delay in older adults (Manning, Stone et al., 1998). More specifically, younger adults (mean age = 21.0) receiving a glucose drink containing 25 g of glucose, either before or after learning a word list, recalled significantly more words after a 25-minute delay and a 24-hour delay compared to participants receiving a drink containing aspartame (Sunram-Lea et al., 2002a). Similarly, a study conducted in older adults (mean age = 67.0) showed that 50 g of glucose administered either before or after hearing a story (logical memory subtest from the Wechsler Memory Scale) significantly improved recall after a 24-hour delay compared to when participants received a saccharin solution (Manning et al., 1992). Furthermore, older adults (mean age = 67.0) manifested increased paragraph recall following a 24-hour delay after ingesting a solution containing 50 g of glucose compared to drinking a saccharin solution, whether glucose was ingested before learning the story or before retrieval (Manning, Stone et al., 1998). The findings from these studies suggest that glucose facilitates encoding, storage and retrieval processes when learning new information. A recent study conducted in younger adults (mean age = 20.00) showed that 25 g of glucose enhanced responses on a word recognition task that were associated with recollection but not responses related to familiarity (Sunram-Lea et al., 2008). Since the former involves the hippocampus, the authors concluded that glucose appears to increase performance on hippocampal-dependent tasks. Using event-related potentials, a study conducted in younger adults (mean age = 28.7) observed a significant effect of glucose ingestion (25 g) on the P3b component, which is related to memory, as evidenced by reduced latency and duration, further confirming glucose facilitation of cognitive functions that rely on the medial temporal lobes (Riby et al., 2008). This study also examined the impact of glucose on the P3a, which is believed to be associated with attention. Although the results failed to reach significance, the authors indicated that results were more variable following glucose ingestion, which may be indicative of an impact of glucose on frontal lobe functioning.

Research has also demonstrated that glucose can significantly enhance other cognitive abilities such as visuospatial memory (Allen et al., 1996; Sunram-Lea et al., 2001, 2002a, 2002b), attention and working memory (Martin & Benton, 1999; Messier et al., 1997; Messier et al., 2003; Scholey et al., 2001; Sunram-Lea et al., 2002b), kinaesthetic memory as measured by a maze task (Scholey & Fowles, 2002), semantic fluency (Riby et al., 2006), phonemic fluency (Allen et al., 1996; Donohoe & Benton, 1999), figural fluency (Allen et al., 1996), divided attention (Kaplan et al., 2000) and facial memory (Metzger, 2000; Metzger & Flint, 2003). However, these results are not consistent across studies (see review of studies on young adults in Appendix A). Furthermore, several studies have also found no effect of glucose on non-memory tasks such as phonemic fluency tasks (Craft et al., 1994; Meikle et al., 2004), measures of visual attention (Flint & Turek, 2003; Meikle et al., 2004), and a verbal working memory measure (Foster et al., 1998). Given these inconsistencies, more research needs to be done using tasks assessing a variety of cognitive domains.

Task difficulty and dual tasks

Several studies have investigated more specifically if the level of difficulty of the task is the mediating factor of glucose facilitation on cognition since glucose has been found to be more effective when cognitive demand is increased (McNay & Gold, 2002). A study conducted in younger adults (mean age = 20.4) varied the degree of difficulty of a task and showed that glucose facilitation only occurred on the more difficult version of the task (Kennedy & Scholey, 2000). More specifically, glucose enhanced performance on the more difficult version of a serial subtraction task (Serial Sevens), which was also identified as being more mentally challenging by the participants, but not on the easier task (Serial Threes). Similarly, another study examining the impact of glucose on the performance of younger adults (mean age = 21.8) on several non-memory tests found that glucose generally reduced the amount of time to solve the more difficult items on a non-verbal performance test, the Porteus Maze (Donohoe & Benton, 1999).

Two studies have examined the impact of glucose on a verbal memory task when a concurrent task is performed during learning trials (Foster et al., 1998; Sunram-Lea et al., 2002b). Younger participants (mean age = 19.5) were administered a modified version of the California Verbal Learning Test which involved learning a list of 20 words (total of five trials) while performing a concurrent motor task which consisted of two-hand sequences (Foster et al., 1998). The first sequence consisted of three-hand movements while the second sequence had four movements. Both sequences had to be done while hearing the list of words, switching sequences every five words. Participants receiving a glucose solution recalled significantly more words on the short and long delay recall trials (free and cued recall) of the CVLT compared to participants receiving a saccharin solution or water. Interestingly, glucose facilitation was not observed on a working memory measure (digit span forward and backward) and on a task assessing visuospatial abilities and visual memory (copy and delayed recall of the Rey-Osterrieth complex figure). Another study conducted in younger adults (mean age = 20.0) used the same list learning task but examined further the impact of dual tasks by incorporating several concurrent tasks (Sunram-Lea et al., 2002b). A key condition interference task (typing sequence of keys as presented on a computer) was used as well as the hand movement sequences (two series of movements performed with both hands), and each concurrent task had to be performed while hearing a list of 20 words. Glucose improved memory performance in both dual-task conditions. However, hyperglycemic facilitation was not observed when participants learned the list of words without having to perform a concurrent task, suggesting that adding a concomitant task was necessary to observe glucose facilitation in this sample of younger adults.

A recent study conducted in younger adults (mean age = 21.60) examined the performance on a word recognition task, with or without a concurrent computer tracking task during auditory presentation of the words, following the ingestion of 25 g of glucose (Scholey et al., 2009). Participants recognized less target words and made more errors in the dual condition, irrespective of drinking solution (glucose or saccharin) and there was no impact of solution on reaction time. However, participants receiving glucose were more accurate on the tracking task compared to those receiving saccharin. The authors indicated that these results suggest that glucose increases attentional resources and that glucose facilitation is observed when there is a high demand placed on these resources.

However, one study found that increasing the level of difficulty of a task did not significantly enhance the glucose facilitation effect on memory compared to the easier version of the task in younger (mean age = 30.1) and older adults (mean age = 68.0) (Riby et al., 2006). Interestingly, both tasks assessing episodic memory and semantic memory were used. The level of difficulty of the episodic memory tasks was manipulated in two ways, either by comparing a task administered with and without a concurrent task (paired associates with a concurrent card-sorting task) or by comparing easier and more difficult items on a task (immediate and delayed recall of concrete and abstract words). Both word and category fluency tasks were administered to measure semantic memory, with easier letters or categories compared to more difficult ones. The researchers (Riby et al.) suggested that the level of difficulty might have been too high to observe glucose enhancement. Similarly, another study in older adults (mean age = 68.75) also failed to find increased glucose facilitation of memory when participants were asked to perform a dual task consisting of sorting cards by colour at the same time as learning a list of word pairs compared to presentation of the paired associates without a second task (Riby et al., 2004). It was proposed that older adults might already be performing at their highest level and that increasing the level of difficulty of a task would therefore not amplify hyperglycemic facilitation. Furthermore, the results of two studies that did not manipulate task difficulty directly by comparing performance in both single and dual task conditions but incorporated difficult tasks in the battery of tests suggest that task difficulty was not a mediating factor for the glucose enhancement effect (Craft et al., 1994; Messier et al., 2003). More specifically, the first study did not observe glucose facilitation on a difficult working memory task, the Paced Serial Addition Test (Craft et al., 1994). The second study used two difficult verbal memory measures, free recall of four lists of 20 words and order recall task consisting of two lists of 20 words with cued recall following presentation (words are provided in alphabetical order and participant is asked to put the words in the order that they were presented) (Messier et al., 2003). A task assessing divided attention, the Modified Brown-Peterson task, was also utilized and consisted of remembering three consonant letters following a delay of 20 seconds during which participants were required to count backwards by threes from a three-digit number. Glucose enhancement was not observed on any of these measures. Therefore, it remains to be examined further whether the effect of glucose will be more observable on tasks that are deemed more difficult, require performing a concurrent task or involve interference.

Glucose regulation

Diabetes has been shown to have a detrimental effect on brain health and is thought to be a risk factor for cognitive impairments (Biessels, Kerssen, de Haan, & Kappelle, 2007), with the risk of dementia being higher in people with diabetes (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006). More specifically, a review of prospective studies conducted primarily in older adults found that those with diabetes had a 1.5 increased risk of cognitive decline and a 1.6 higher risk of developing dementia compared to non-diabetics (Cukierman, Gerstein, & Williamson, 2005). Given that the prevalence of diabetes has substantially increased, with older adults being more vulnerable (Morley, 2008), this disease is increasingly becoming a public health concern.

Diabetes and cognition. A meta-analysis of 33 studies investigating cognitive functioning in participants with type 1 diabetes concluded that compared to healthy controls, participants with type 1 diabetes obtained lower scores on measures of intelligence, psychomotor and processing speed, attention, cognitive flexibility and visual perception whereas no difference was found on measures of learning and memory as well as tasks assessing language (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). A recent study examined several factors that could potentially account for the cognitive deficits observed in patients with type 1 diabetes (Brismar et al., 2007). The factors studied included duration of diabetes, age at onset of diabetes, hypoglycemic episodes, hypoglycemic comas, mean HbA1c levels, retinopathy, nephropathy, peripheral neuropathy, sensory nerve conduction, motor nerve conduction, hypertension as well as gender, age, height, and body mass index. The findings of this cross-sectional study suggest that duration of diabetes and age at onset were the predictors most frequently associated with decreased performance on cognitive measures assessing a variety of cognitive domains. More specifically, longer duration of diabetes was a significant predictor of reduced performance on the following cognitive domains: psychomotor speed (Digit Symbol-Coding from the WAIS-R, Grooved Pegboard Test and Trail Making Test Part B), memory (Claeson-Dahl's test of learning and memory, Digit Symbol-Coding incidental learning from the WAIS-R, Rey Complex Figure Test immediate recall, delayed recall and recognition), and executive functions (Controlled Oral Word Association FAS, Zoo Map Test and Trail Making Test Part B). Younger age at onset of diabetes significantly predicted poorer performance on processing speed (Digit Symbol-Coding from the WAIS-R, Paced Auditory Serial Attention Test, Trail Making Test Part B), attention (Digit Span Forward from the WAIS-R, Block Span Forward from the WAIS-R, Paced Auditory Serial Attention Test), working memory (Block Span Backward from the WAIS-R, Digit Span Backward from the WAIS-R, Paced Auditory Serial Attention Test), and language (Controlled Oral Word Association FAS, Vocabulary from the WAIS-R). A review of the literature concluded that hypoglycemic episodes do not appear to have a negative impact on cognition (Wessels, Scheltens, Barkhof, & Heine, 2008). However, it was proposed that microvascular disease in the brain secondary to hyperglycemia could underlie the cognitive impairments observed in people with type 1 diabetes. Recent studies have used imaging techniques to examine whether cognitive impairments are associated with brain abnormalities (Brands et al., 2006; Kodl et al., 2008; Wessels et al., 2007). When comparing participants with type 1 diabetes presenting with retinopathy (mean age = 42.3) compared to type 1 diabetics without retinopathy (mean age = 42.1) and non-diabetic controls (mean age = 40.9), diabetics with retinopathy had significantly reduced white matter volume compared to controls (Wessels et al., 2007). No significant difference was observed between the other groups. Furthermore, diabetics with retinopathy obtained lower scores on tasks assessing speed of information processing (Trail Making Test Part A, The Stroop Colour Word Test Part 1 and 2 and the Symbol Substitution coding from the WAIS) compared to controls whereas diabetics without retinopathy performed more poorly on tasks of visuoconstruction (Rey Complex Figure Test copy, Block Design from the WAIS) compared to controls. Findings also indicated a positive correlation between performance on tasks measuring speed of information processing, attention and executive functioning and white matter volume. The authors concluded that cognitive impairments in type 1 diabetics can therefore be partially explained by microvascular complications. Another study conducted in older participants (mean age = 60.9) with type 1 diabetes did not observe any difference between diabetics and controls on any of the MRI measures, including deep white-matter lesion, periventricular white-matter lesion, cortical atrophy and subcortical atrophy (Brands et al., 2006). Furthermore, cognitive performance of participants with type 1 diabetes was only significantly decreased on information processing speed compared to controls. A study using diffusion tensor imaging showed that participants with type 1 diabetes (mean age = 45.1) had white matter microstructure abnormalities compared to controls, more specifically in the posterior corona radiata and the optic radiation, and these impairments were associated with decreased performance on a visual-spatial construction task (Rey-Osterrieth Complex Figure Test) and a measure of fine motor dexterity (Grooved Pegboard) (Kodl et al., 2008). Reduced neurogenesis in the dentate gyrus and increased response latency on a conditioned active avoidance task has been observed in an animal model of type 1 diabetes (Alvarez et al., 2009). Treatment with continuous subcutaneous insulin infusion in children with type 1 diabetes (mean age = 12.9) during a period of 6 to 8 weeks resulted in improved normalization of glucose levels, mood (self, parent and teacher reports), behaviour (reduction in problems according to parents), and performance on cognitive tasks assessing perceptual ability, selective and divided attention, cognitive flexibility and working memory (Knight et al., 2009). Overall, research on the neuropsychological functioning of adults with type 1 diabetes suggests a pattern of mild cognitive decline.

Findings from cross-sectional studies have shown that adults with type 2 diabetes perform more poorly than controls on measures of overall cognitive functioning as assessed by a screening task or represented by a composite score (Cukierman-Yaffe, Gerstein, Anderson et al., 2009; Ebady, Arami, & Shafigh, 2008; Tiehuis, Vincken et al., 2008), simple visual attention (Paile-Hyvarinen et al., 2009), working memory (Paile-Hyvarinen et al., 2009), learning and memory (Brands, Van den Berg et al., 2007; Manschot et al., 2008; Paile-Hyvarinen et al., 2009; Ruis et al., 2009), information processing speed (Brands, Van den Berg et al., 2007; Manschot et al., 2008; Saczynski et al., 2008; van den Berg et al., 2008; Yeung, Fischer, & Dixon, 2009), complex attention/executive function (Brands, Van den Berg et al., 2007; Manschot et al., 2008; van den Berg et al., 2008; Yeung et al., 2009) and motor dexterity (R. Kumar, Anstey, Cherbuin, Wen, & Sachdev, 2008). Although a study found no significant difference between the performance of participants with type 1 diabetes (mean age = 60.9) and type 2 diabetes (mean age = 61.5) on reasoning, memory, information processing speed, visual construction and complex attention/executive function tasks (Brands, Biessels et al., 2007), according to a recent review, the cognitive domains that are the most consistently reduced across studies appear to differ slightly depending on the type of diabetes (Kodl & Seaquist, 2008). More specifically, type 1 diabetes is associated with decrements in attention, information processing speed, psychomotor efficiency, visual construction and cognitive flexibility, whereas type 2 diabetes is mostly related to decreased memory, psychomotor speed and executive function. Increased rates of cognitive decline have also been reported in older adults with type 2 diabetes (Bruce, Davis, Casey, Starkstein, Clarnette, Almeida et al., 2008; Maggi et al., 2009), and according to one study, race differentially affects cognitive decline in men with type 2 diabetes, with African Americans showing a sharper reduction in cognitive performance with age than Caucasians (Obidi et al., 2008). Poorer cognitive functioning at 11 years of age has been shown to increase the risk of type 2 diabetes after 16 years of age (Olsson, Hulting, & Montgomery, 2008). As mentioned previously, research has shown that cognitive impairments associated with type 2 diabetes are more prominent in older adults (Awad, Gagnon, & Messier, 2004; Ryan & Geckle, 2000) and that type 2 diabetes increases the risk of dementia, including Alzheimer's disease (see reviews by Biessels & Kappelle, 2005; Messier, 2003). A review of cross-sectional studies that examined the impact of type 2 diabetes on cognition found that impairments were more consistent on measures of verbal memory and processing speed and that the largest impairments were observed in studies in which participants are older (mean age = 65) and have highest blood glucose levels as measured by higher glycosylated hemoglobin (Awad, Gagnon et al., 2004). Another review of studies examining the relationship between type 2 diabetes and cognitive performance revealed that findings from 13 studies out of 19 reported cognitive impairments in type 2 diabetics (Strachan, Deary, Ewing, & Frier, 1997), with deficits in verbal memory being the most often documented. The authors highlighted that a variety of different cognitive tests (>70) have been used in the studies reviewed and that a uniform battery of tests would facilitate comparisons across studies. Ryan and Geckle (2000) also reviewed articles that examined the relationship between Type 2 diabetes and cognitive functioning. Whereas learning and memory impairments are rarely observed in middle-aged adults with diabetes, older diabetics appear to manifest decline in that cognitive domain. The authors suggest that diabetes coupled with age-associated changes such as diminished hippocampal volume could explain why it seems that memory is impaired only in older diabetics as supported by the threshold theory. Thus, older adults would be more susceptible to impairments in memory and learning when developing diabetes because it would be combined with preexisting age-associated changes. Interestingly, a study conducted in diabetics 85 years of age showed that although cognitive deficits were observed on a measure of attention and a task assessing speed of information processing compared to controls at baseline, decline in cognitive performance was not more pronounced in the diabetes group compared to controls when participants were retested yearly up until 90 years of age (van den Berg, de Craen, Biessels, Gussekloo, & Westendorp, 2006). Therefore, it was suggested that increased cognitive decline associated with diabetes in older adults is less apparent in the oldest age bracket.

Studies have also used imaging techniques to identify changes in the brains of middle-aged and/or older adults with type 2 diabetes (den Heijer et al., 2003; Elderkin-Thompson, Hellemann, Gupta, & Kumar, 2009; S. M. Gold et al., 2007; Jongen et al., 2007; A. Kumar, Gupta, Thomas, Ajilore, & Hellemann, 2009; A. Kumar et al., 2008; R. Kumar et al., 2008; Last et al., 2007; Manschot et al., 2007; Manschot et al., 2008; Soininen, Puranen, Helkala, Laakso, & Riekkinen, 1992; Tiehuis, van der Graaf et al., 2008; van Harten et al., 2007). Using computed tomography, diabetics who were taking medication (mean age = 77.6) had significantly more central temporal lobe atrophy, more specifically larger right temporal horn, compared to controls (mean age = 74.0) whereas no difference was observed between diabetics who were being treated with diet alone (mean age = 76.0) compared to controls (Soininen et al., 1992). Studies using magnetic resonance imaging demonstrated that type 2 diabetics have significantly more total brain atrophy (R. Kumar et al., 2008), cortical atrophy (Last et al., 2007; Manschot et al., 2007; Manschot et al., 2008), subcortical atrophy

(Last et al., 2007; Manschot et al., 2007; Manschot et al., 2008), white matter lesions/deep white matter lesions (Jongen et al., 2007; Manschot et al., 2007; Manschot et al., 2008), decreased gray matter volume (Jongen et al., 2007; A. Kumar et al., 2008), and increased lateral ventricle volume (Jongen et al., 2007), cerebrospinal fluid volume (R. Kumar et al., 2008), hippocampal atrophy (den Heijer et al., 2003; S. M. Gold et al., 2007), as well as amygdalar atrophy (den Heijer et al., 2003). Magnetization transfer ratios have also been shown to be lower in the head of the caudate nucleus in participants with both type 2 diabetes and depression compared to non-depressed type 2 diabetics and controls, with the latter group having significantly higher values (A. Kumar et al., 2009). Similarly, another study observed the same pattern of results across the three groups, with magnetization transfer ratios of the caudate being substantially below in the diabetics with depression, and non-depressed diabetics having intermediate values (Elderkin-Thompson et al., 2009). There was also an association between these values and overall cognitive performance. These two studies suggest that cognitive impairment and depressed mood observed in adults with type 2 diabetes could be related to abnormalitites in the caudate nucleus. When examining the relationship between results obtained on imaging and neuropsychological measures, periventricular hyperintensities were associated with motor speed as assessed by the Grooved Pegboard Test (van Harten et al., 2007). However, deep white matter lesions, medial temporal lobe atrophy, cerebral atrophy and lacunar infarcts were not related to decreased performance on measures assessing executive functioning, speed of information processing and motor speed. Another study demonstrated deficits on memory measures and hippocampal atrophy in diabetics (mean age = 59.2) compared to controls (mean age = 59.9), although correlations between these measures were non-significant. Therefore, brain pathology is present in middle-aged and older diabetics albeit not always associated with deficits observed on neuropsychological measures.

Several studies have examined the association between diabetes and dementia, including Alzheimer's disease (Brayne et al., 1998; Bruce, Davis, Casey, Starkstein, Clarnette, Foster et al., 2008; Bruce, Harrington, Davis, & Davis, 2001; Curb et al., 1999; Heitner & Dickson, 1997; Irie et al., 2008; Leibson et al., 1997; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; MacKnight, Rockwood, Awalt, & McDowell, 2002; Nielson et al., 1996; Ott et al., 1996; Ott et al., 1999; Peila, Rodriguez, & Launer, 2002; Rajakumaraswamy, Rajapakse, & Fernando, 2008). Although studies have reported a significant relationship between diabetes and Alzheimer's disease (Brayne et al., 1998; Irie et al., 2008; Ott et al., 1996; Ott et al., 1999; Peila et al., 2002), other studies did not find an association (Curb et al., 1999; Luchsinger et al., 2001; MacKnight et al., 2002). One study observed a significantly increased risk of Alzheimer's disease in diabetic men but not in diabetic women compared to non-diabetics (Leibson et al., 1997) and another noted that diabetes is infrequently observed in Alzheimer's disease (Nielson et al., 1996). Two studies explored the presence of senile plaques and neurofibrillary tangles, pathology related with Alzheimer's disease, in older participants with diabetes compared to non-diabetics (Heitner & Dickson, 1997; Peila et al., 2002). In the first study, the amount of neurofibrillary tangles in the hippocampus and the entorhinal cortex, the stage of neurofibrillary tangles and the senile plaque score did not differ between both groups (Heitner & Dickson, 1997). Similarly, the second study did not observe an increased risk of neurofibrillary tangles in the hippocampus and cortex, neuritic plaques and cerebral amyloid angiopathy in diabetics compared to non-diabetics (Peila et al., 2002). However, when ApoE genotype was considered, the results indicated that the combination of diabetes and ApoE4 resulted in a significant increased risk of neuritic plaques, neurofibrillary tangles and amyloid angiopathy, suggesting a possible interaction between diabetes and Alzheimer's disease. The combination of diabetes and ApoE4 has been shown to increase the risk of developing Alzheimer's disease and mixed dementia above that of each factor individually (Irie et al., 2008). Even though results are not always consistent across studies, the overall finding is that type 2 diabetes increases the risk of dementia, including Alzheimer's disease (see reviews by Luchsinger & Gustafson, 2009; Roriz-Filho et al., 2009; Strachan, Reynolds, Frier, Mitchell, & Price, 2008). One study also investigated whether mild cognitive impairment (MCI), an intermediate stage between normal cognitive functioning in aging and dementia, is associated with diabetes (Roberts et al., 2008). A diagnosis of diabetes before the age of 65, duration of diabetes of at least 10 years, insulin treatment and diabetes-related complications (neuropathy, retinopathy and/or nephropathy) were all found to be related with MCI.

Although research has shown an association between type 2 diabetes and cognitive decline, the mechanisms underlying this relationship remain unclear and are likely multifactorial, including hyperglycemia (Cukierman-Yaffe, Gerstein, Williamson et al., 2009; Kodl & Seaquist, 2008; Strachan, Price, & Frier, 2008; Strachan, Reynolds et al., 2008; Strachan, Reynolds, Frier, Mitchell, & Price, 2009), recurrent hypoglycemic episodes (Strachan, Reynolds et al., 2008), genetics (Strachan, Price et al., 2008; Strachan et al., 2009), hypertension (Strachan, Price et al., 2008; Strachan, Reynolds et al., 2008), dyslipidemia (Strachan, Price et al., 2008), hyperinsulinemia/insulin resistance (Kodl & Seaquist, 2008; Strachan, Reynolds et al., 2008; Strachan et al., 2009), microvascular disease (Kodl & Seaquist, 2008; Strachan, Reynolds et al., 2008; Strachan et al., 2009), macrovascular disease (Kodl & Seaquist, 2008; Strachan, Price et al., 2008; Strachan, Reynolds et al., 2008; Strachan et al., 2009; Umegaki et al., 2008), depression (Strachan, Price et al., 2008; Strachan, Reynolds et al., 2008; Strachan et al., 2009), medications (Strachan, Price et al., 2008; Strachan, Reynolds et al., 2008; Strachan et al., 2009), increased glucocorticoids due to activation of the hypothalamic-pituitary-adrenal axis (Strachan, Reynolds et al., 2008; Strachan et al., 2009), and increased inflammation (Strachan, Reynolds et al., 2008). A study conducted in older women without diabetes (mean age = 64.2) showed that increased fasting insulin levels resulted in more pronounced decline over a period of 4 years on a screening measure of cognitive functioning and a composite score of verbal episodic memory (van Oijen et al., 2008). Increased body mass index has also been associated with reduced gray matter volume in men but not in women (Taki et al., 2008) and elevated adiposity, a risk factor for type 2 diabetes, has been shown to be related with increased risk of dementia, particularly when adiposity is higher in middle age (Luchsinger & Gustafson, 2009). In a sample of older diabetics (mean age = 76.0), diabetes duration and peripheral arterial disease significantly predicted dementia after a mean follow-up of 7.6 years, and the former was associated with Alzheimer's disease (Bruce, Davis, Casey, Starkstein, Clarnette, Foster et al., 2008). Similarly, in a large sample (n = 958) of adults with type 2 diabetes (mean age = 68.9), increased duration of diabetes was associated with more pronounced decline over a period of 2 to 4 years compared to controls on a cognitive screening measure, a composite score of overall cognitive functioning, a composite score of verbal episodic memory and semantic fluency (Okereke et al., 2008). Furthermore, participants with type 2 diabetes who exhibited reduced blood glucose levels during cognitive testing demonstrated superior phonemic fluency and visual-motor tracking/ cognitive flexibility skills compared to participants whose glucose levels increased during testing, suggesting more efficient use of glucose (Galanina, Surampudi, Ciltea, Singh, & Perlmuter, 2008). Participants with type 2 diabetes and symptomatic arterial disease performed more poorly on measures of attention, memory and visuospatial construction compared to participants with only arterial disease, suggesting that diabetes has an impact on cognitive functioning above and beyond vascular-related cognitive decline (Tiehuis et al., 2009). It has been proposed that pronounced cognitive impairments are only observable in children who developed type 1 diabetes at a young age (below 7 years of age) and in older adults (above 65 years of age) with type 2 diabetes (Biessels, Deary, & Ryan, 2008). Hence, comorbidities associated with diabetes, age of onset and duration appear to contribute to diabetes-related cognitive decline.

Six studies have examined the cognitive performance of older people with type 2 diabetes before and after the start of treatment to reduce blood glucose levels (Gradman, Laws, Thompson, & Reaven, 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993; Mussell, Hewer, Kulzer, Bergis, & Rist, 2004; Naor, Steingruber, Westhoff, Schottenfeld-Naor, & Gries, 1997; Ryan et al., 2006; Wu et al., 2003). See Appendix C for a summary of the results of these studies. Although one study failed to show cognitive improvement following treatment (Mussell et al., 2004), the results of the other studies suggested that reducing blood glucose levels improved performance on some tasks, including learning and memory. More specifically, one study demonstrated that verbal memory, as measured by the Buschke Selective Reminding Test, was significantly enhanced over a period of seven months (baseline, one month, three months and seven months) when older diabetics were given glipizide one month after stopping any previous treatment that they had been taking for diabetes (Gradman et al., 1993). Recall was significantly increased in participants that were already taking medication for diabetes before participating in the study (mean age = 67.1) following two months of glipizide and in participants not on any diabetic treatment (mean age = 69.4) after six months of glipizide. Furthermore, blood glucose levels decreased significantly after two months of taking glipizide in both diabetic groups. No change in performance on the cognitive tasks was observed in the control group. Finally, there was no significant effect of treatment on measures of attention as well as on tasks of complex and simple perceptual motor functions in both diabetic groups. Another study demonstrated improved performance on tasks assessing attention and concentration (Grooved Pegboard, interference task from the Stroop Colour and Word Test), memory (cued recall task) and problem solving (Picture Arrangement subtest from the WAIS-R) in older diabetics (mean age = 71.0) following a 6-month treatment consisting of oral hypoglycemic medications compared to performance at baseline (Meneilly et al., 1993). Again, this improvement on neuropsychological measures paralleled a significant decline in blood glucose levels. However, this study did not include a control group. Therefore, the possibility that the observed improvement on the cognitive measures being associated with practice effects cannot be ruled out. Performance on tasks assessing mental status and psychomotor speed during the 6-month follow-up was not significantly different from baseline. When comparing an intensive treatment consisting of an inpatient program that targeted diet, blood glucose monitoring and included an educational component coupled with glibenclamide or insulin therapy, to a regular treatment (participants continued their current therapy while being on a wait list), improvements were only observed in the group receiving intensive treatment on measures of concentration and psychomotor speed (Naor et al., 1997). Participants were tested at baseline, approximately two weeks later (discharge for participants in the intensive treatment group) and again six weeks later (following discharge for participants in the intensive treatment group). Interestingly, levels of glycosylated hemoglobin decreased over time in both groups. Two other studies using bigger samples also demonstrated improved cognitive performance in older adults receiving diabetic treatment (Ryan et al., 2006; Wu et al., 2003). In one study, older adults with type 2 diabetes were given either a combination of metformin and rosiglitazone (n = 69; mean age = 60.7) or metformin and glyburide (n = 72; mean age = 59.6) and were tested on cognitive measures at baseline and 24 weeks after initiation of treatment (Ryan et al., 2006). In both treatment groups, improvements were observed on a working memory measure (Paired Associates Learning from the Cambridge Neuropsychological test Automated Battery), with fasting glucose levels being significantly reduced and this reduction being associated with increased cognitive perfomance on the working memory task. In the second study, a distinction was made according to length of time since diabetes diagnosis (Wu et al., 2003). Participants were divided in two groups, those who had been diagnosed five or less years ago (n = 381) and those who received the diagnosis over five years ago (n = 337). These two groups were further divided in two, i.e. participants who were being treated (≤5 years: mean age = 70.6; >5years: mean age = 70.6) and those who were not receiving any treatment (≤5 years: mean age = 70.6; >5years: mean age = 69.8). Participants who were being treated were either taking oral hypoglycemic medications or insulin. Results suggested that the cognitive performance of participants receiving treatment had deteriorated less over a two-year period compared to those not receiving treatment as measured by a cognitive screening measure (Modified Mini-Mental State Exam). Furthermore, this impact was more pronounced in the group with the longest diabetes duration. Interestingly, participants' self-report of activities of daily living and instrumental activities of daily living revealed that participants being treated for diabetes reported less change in functioning.

Impaired glucose tolerance/altered glucose regulation. Impaired glucose tolerance has been shown to adversely affect cognition in both young and older adults with the cognitive impairments being more pronounced in older adults (see reviews by Lamport, Lawton, Mansfield, & Dye, 2009; Messier, 2005; Messier & Gagnon, 2000). Several studies have examined the impact of poor glucose regulation in older participants who either met criteria for impaired glucose tolerance (Hiltunen, Keinanen-Kiukaanniemi, & Laara, 2001; Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Lindeman et al., 2001; Vanhanen et al., 1998) or who tended to have higher blood glucose following a glucose load (Convit, Wolf, Tarshish, & de Leon, 2003; Kaplan et al., 2000; Messier et al., 1997; Messier et al., 2003). A summary of the results of these studies is presented in Appendix B. In general, previous research demonstrated that impaired glucose regulation or poorer glucose regulation is associated with cognitive deficits including significant memory decline in older participants (above 60 years of age). More specifically, population studies have shown that older adults with impaired glucose tolerance obtained lower scores on a cognitive screening measure, the Mini-Mental State Examination, compared to participants with normal glucose tolerance (Hiltunen et al., 2001; Kalmijn et al., 1995; Vanhanen et al., 1998). Furthermore, performance was also worse on a memory measure, more specifically the long-term recall portion of the Buschke Selective Reminding Test (Vanhanen et al., 1998). In contrast, one study failed to find decreased cognitive performance in the impaired glucose tolerance group compared to participants with normal glucose tolerance (Lindeman et al., 2001). However, the administration of the battery of cognitive tests was done approximately one to two hours after participants had ingested 75 g of glucose. In a study conducted in both middle-aged and older adults, increased blood glucose levels, both at fasting and two hours following a 75 g glucose load, were associated with reduced episodic memory, although this was only observed in women (Rolandsson, Backestrom, Eriksson, Hallmans, & Nilsson, 2008). According to a recent review of the literature, impairments in verbal memory have been the most consistently reported across studies (Lamport et al., 2009). Studies have shown that the ingestion of glucose can attenuate some of the cognitive impairments observed in older adults with poor glucose regulation (Kaplan et al., 2000; Messier et al., 1997; Messier et al., 2003). More specifically, improvements were observed on tasks of memory and attention after participants (mean age = 62.3) were given a drinking solution containing 50 g of glucose (Messier et al., 1997). This was also observed following ingestion of other carbohydrates (50 g), either potatoes or barley (Kaplan et al., 2000). Furthermore, when dividing older participants (age range = 55-84) using a median of 72, the oldest old group with worse glucoregulation obtained lower scores on tasks measuring working memory, verbal episodic memory and executive functioning after drinking the saccharin solution. However, glucose ingestion reduced the observed impairments on those tasks except for the task used to assess executive functioning (Messier et al., 2003). Overall, peripheral glucose regulation appears to interact with cognitive functions in older people, particularly in the oldest age bracket. Finally, a study reported an association between high blood glucose levels two hours after an intravenous glucose tolerance test in non-diabetics and a diminished size of the hippocampus, a brain structure associated with memory (Convit et al., 2003). Thus, impaired glucoregulation seems related to changes in the size of the hippocampus.

Objectives and hypotheses

The main objective of this study was to investigate further the impact of ingested glucose on cognition in older adults by addressing three research focuses. The first objective was to examine the impact of three doses of glucose (300 mg/kg, 650 mg/kg and 1 g/kg) adjusted to body weight on performance on neuropsychological tasks assessing working memory, verbal memory, executive functioning and fine motor skills since there is a paucity of research on glucose and cognition in humans with adjusted glucose dose to body weight even though research on animals has demonstrated that there is a dose-response curve. Based on previous research on absolute doses of glucose, it was hypothesized that higher doses of glucose would be more effective in this sample of older adults. The second objective was to include cognitive measures involving a concomitant or interference task in the battery of tests to examine whether the glucose facilitation effect will be more readily observable on tasks that require dual processing since research in younger adults has shown that hyperglycemic enhancement can be more pronounced on measures that involve a secondary task. It was expected that the glucose improving effect would be more readily observable on tasks that require dual processing. Thirdly, the effect of glucoregulation was evaluated since impaired glucose tolerance has been associated with cognitive impairments, particularly in older adults, and glucose ingestion can reduce these deficits. Therefore, this study examined whether glucoregulation mediated the impact of glucose on cognitive performance and if age interacted with glucoregulation. Based on past research, it was expected that older adults categorized as worse regulators would perform more poorly on the cognitive tasks compared to better regulators and that glucose facilitation would be more observable in older adults who regulate glucose more poorly.

Method

This research project has been approved by the Research Ethics Board of the University of Ottawa (see Appendix D).

Participants

Recruitment. Participants were recruited through local magazine and newspaper advertisements and via posters placed in various places in the community (e.g. community centres, recreational centres, retirement residences, apartment buildings, and golf clubs) and on local websites aimed at seniors. See Appendix E for the ad that was used.

Inclusion and exclusion criteria. Participants had to be 60 years of age or older to be included in the study. Although previous research on the impact of glucose on cognition in older adults have used cutoffs of 55 (Messier et al., 1997; Messier et al., 2003), 58 (Gonder-Frederick et al., 1987; Hall et al., 1989) or 60 years of age and over (Allen et al., 1996; Kaplan et al., 2000; Manning, Stone et al., 1998; Parsons & Gold, 1992; Riby et al., 2004), a cutoff of 60 was chosen since cognitive impairments associated with poorer glucoregulation have been observed in the oldest bracket of this age group (Messier et al., 2003). Exclusionary criteria included hypoglycemia (because of the fasting requirement), diabetes, chronic hepatitis, excessive alcohol consumption which was operationally defined as four or more drinks per day for at least one month (Gastfriend, Garbutt, Pettinati, & Forman, 2007; Skinner, Holt, Schuller, Roy, & Israel, 1984), drug abuse (daily intake of cannabis or current use of other recreational drugs, irrelevant of frequency), or any brain disorder including cerebral hemorrhage, tumors, or lesions. Participants who reported a loss of consciousness for more than one hour were excluded. Participants who were currently suffering from depression were excluded as depression has been associated with cognitive impairments (see reviews by Elliott, 1998; Henry & Crawford, 2005). Furthermore, participants who were consulting a psychiatrist at the time of the screening or currently taking psychiatric medication were not included. These criteria were chosen because they could have potentially affected blood glucose levels and hence, glucose regulation, and/or performance on the cognitive measures. Participants could not suffer from colour-blindness because one of the cognitive tasks used, the Stroop Colour and Word test, requires intact colour vision. A telephone interview was conducted to screen participants and ensure that they met the criteria established for this study (see Appendix F). This questionnaire also examined participant's self-report memory status for an overall screening of memory problems. Participant's age and gender were also noted during the screening interview. In the event that a potential participant did not meet criteria to be included in the study, their answers were destroyed.

The Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) was used to further screen for depression when participants came to the laboratory for the first visit. The BDI-II was selected because of its simplicity of administration, scoring and interpretation. Internal consistency is good (.84 to .93) and the BDI-II has been found to correlate strongly with other measures used to assess depressive symptomatology (Strauss, Sherman, & Spreen, 2006). This measure comprises 21 questions that are in accordance with depressive symptomatology as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (2000) and for each question, there are four levels of intensity, total scores being between 0 and 63 (McDowell, 2006). Participants with a score higher than 13/63 would have been excluded since scores between zero and 13 represent the minimal depression range (McDowell, 2006). The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was used to screen for cognitive deficits. The MMSE was selected because it has been found to be sensitive to dementia (Strauss et al., 2006). This screening measure briefly evaluates orientation to time and place, registration and recall of three objects, attention and calculation (counting backward by sevens or spelling a word backward), language (naming two items, repeating a phrase, following a verbal command as well as a visually presented command and writing a sentence) and construction (copying a design) (McDowell, 2006). A score below 24/30 on the Mini-Mental Status Examination would have resulted in exclusion from the study. However, none of the participants included in this study following the telephone screening interview met exclusionary criteria based on their scores on the BDI-II and the MMSE.

Procedure

The overall timeline of the study is presented in Appendix G. Participants were asked to arrive fasted for both testing sessions. Fasting was defined as nothing to eat or drink, except water, after 12h00 a.m. This fasting procedure has been used in previous research on glucose and cognition (Awad et al., 2002; Ford, Scholey, Ayre, & Wesnes, 2002; Foster et al., 1998; Hall et al., 1989; Kennedy & Scholey, 2000; Manning et al., 1992; Meikle et al., 2004, 2005; Messier et al., 1999; Messier et al., 1997; Messier et al., 2003; Parsons & Gold, 1992; Riby et al., 2006; Scholey et al., 2001; Sunram-Lea et al., 2001). Participants were contacted the day before each session was scheduled to remind them of their appointment and the fasting procedure. Each session was scheduled in early morning, starting between 8h00 and 10h00, at the convenience of the participants. Before starting the session, participants were asked whether they had anything to eat or drink (except water) since midnight to confirm that they had been fasting. In the event that participants reported feeling weak or faint at any time during the session, fruit juices and cereal bars were available to these participants. Furthermore, in the event that a participant mentioned feeling weak from fasting, they would have been monitored and not dismissed before they reported feeling better. However, none of the participants tested reported such symptoms.

Upon arrival at the memory laboratory for the first visit, an informed consent was obtained from each participant after the nature and possible consequences of the study had been explained and participant's questions and/or concerns had been addressed (see Appendix H). During this initial visit, the MMSE and BDI-II were administered to ensure that participants were eligible to participate in the study. Weight and height were measured to calculate body mass index and information on smoking (currently smoking or not), physical exercise (calculated as the average amount of exercise per week in minutes) as well as history of diabetes in immediate family (whether one or both parents suffered from diabetes) were collected due to identification as associated risk factors for altered glucoregulation (Eriksson & Lindgarde, 1996; Shaten, Smith, Kuller, & Neaton, 1993). The Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) was also administered. This test was designed for the estimation of premorbid intellectual functioning of adults aged 16-89 years (internal consistency = .90-.97; test-retest reliability = .90-.94). It requires the examinee to read and pronounce 50 words that have irregular grapheme to phoneme translation. This test is based on a reading-recognition paradigm that involves the reading and pronunciation of words that can only be read correctly if the person knows and recognizes them in their written form. The WTAR was used to control for possible difference of crystallized intelligence between groups. Information on education level was also obtained to calculate the total number of years of schooling completed. One year part-time was counted as half a year full-time.

Three experimental groups were constituted based on the dose of glucose participants received. Participants were randomly assigned to one of three doses of glucose and the amount of glucose solution given to each participant was adjusted to one of three doses, i.e. 300 mg/kg, 650 mg/kg or 1 g/kg of glucose. These doses of glucose were chosen because doses of 25, 50 and 75 g have shown the cognitive enhancing effect of glucose and would approximately be 300 mg/kg, 650 mg/kg or 1 g/kg in someone weighing 75 kg (Messier, 2004). Half the participants randomly received the placebo solution on the first visit and the glucose solution on the second visit and the other half were administered the reverse order to control for order effects. The placebo solution consisted of 211 mg of saccharin and 3 g of unsweetened, lemonade Kool-Aid (Kraft Foods North America) in one litre of water (Awad et al., 2002; Messier et al., 2003). The glucose solution consisted of a lemon-flavoured solution containing 220.1 g of glucose, 17.6 mg of saccharin and 3 g of unsweetened, lemonade Kool-Aid in one litre of water based on the methodology previously used by Messier et al. (1998). Saccharin was added to the glucose drink to make the taste of the two solutions comparable in order for the participants to be blind to the solution ingested. It is important that participants be unaware of the specific drinking solution ingested during a testing session since being merely informed beforehand of the glucose solution has been shown to enhance cognition (Green, Taylor, Elliman, & Rhodes, 2001). During each visit, the amount of solution given to each participant was calculated based on their weight and the dose of glucose (see Appendix I for the calculation sheet used).

During both visits, a battery of tests assessing attention, memory, motor skills and executive functions was used to evaluate the participant's cognitive functioning. The two visits were separated by at least 10 days to minimize interference from one session to the other. Cognitive testing started 15 minutes after drinking the sweet solution to ensure that glucose had reached the bloodstream (Benton & Owens, 1993). All participants were offered juice and a cereal bar after the conclusion of each session. At the end of the second testing session, participants were asked what solution they thought they drank during that second session, either real sugar or artificial, to ensure that they were blind to the solutions ingested. Participants were then told which solution they received during each visit. Each participant received 20$ for participating in the study and parking was compensated.

Blood glucose measurements were obtained before drinking the sweet solution and 30 minutes and 2 hours following the ingestion of the solution. A small drop of blood was obtained from a fingertip using a disposable Glucolet lancing device (Bayer, Canada) and blood glucose was measured using an Elite glucometer (Bayer, Canada). Based on the blood glucose measurements, glucose tolerance was estimated and each group was further divided in better glucose regulators and poorer glucose regulators. Participants were categorized as better or worse glucose regulators based on the glucose recovery index (Craft et al., 1994; Messier et al., 1999; Messier et al., 1997; Messier et al., 2003). The recovery index was obtained by subtracting the baseline blood glucose measurement from the 2-hour blood glucose measurement. A median split was then used for each of the three experimental groups to separate the good glucoregulators (lower recovery scores) and the bad glucoregulators (higher recovery scores).

Cognitive measures

The cognitive tasks were partly chosen based on measures that were used in previous studies on the glucose facilitation effect on cognition and research examining the impact of dual processing on this effect. They were also chosen to ensure a variety of cognitive domains and dual tasks. The neuropsychological battery was administered in a specific order (see Table 1) because two verbal memory tasks (list learning and paragraph recall) require delayed recall within a specific time frame and nonverbal tasks have to be administered during the delay for the list learning task (Strauss et al., 2006). Furthermore, research has shown that the timing of administration of a task after drinking a glucose solution is not related to blood glucose levels (Messier et al., 1998; Messier et al., 2003). The instructions for each test were written to ensure standardization of administration (see Appendix J). The administration of the battery of tests was conducted by one of three testers which included the author and two research assistants. Both testing sessions for a participant were completed by the same tester to ensure consistency. The research assistants were not involved in the scoring of the measures. The neuropsychological tests can be grouped into four cognitive domains.

Table 1

Order and Timing of Blood Glucose Measurements, Drinking Solution and Neuropsychological Tasks

Time	Blood glucose	Drinking solution	Neuropsychological task
0 min	First		
		Glucose or saccharin	
15 min			CVLT-II Immediate recall with interference task and short-delay recall
30 min	Second		
			Spatial Span
			Grooved Pegboard with interference task
45-55 min			CVLT-II Delayed recall and recognition
			Modified Brown Peterson Task
			Logical Memory Immediate recall
			Arithmetic
			Stroop Colour and Word Test
			Digit Span
			Letter-Number Sequencing
85-115 min			Logical Memory Delayed recall and recognition
120 min	Third		

Note. CVLT-II = California Verbal Learning Test-Second Edition

Measures of attention and working memory. Previous research has shown that poor glucoregulation reduces performance on tasks assessing working memory, more specifically the Arithmetic, Digit Span and Letter-Number Sequencing subtests of the WAIS-III (Wechsler, 1997a) and the Spatial Span subtest of the WMS-III (Wechsler, 1997b) in older participants (Messier et al., 2003). Furthermore, several studies found a significant improvement in working memory following glucose ingestion (Hall et al., 1989; Kennedy & Scholey, 2000; Scholey et al., 2001; Sunram-Lea et al., 2002b) while others did not observe the facilitation effect of glucose on this cognitive domain (Foster et al., 1998; Sunram-Lea et al., 2001, 2002a, 2004). Hence, working memory was assessed using the subtests in the Working Memory indices of the WAIS-III (Wechsler, 1997a) and the WMS-III (Wechsler, 1997b): Arithmetic (internal consistency = .77-.91; test-retest reliability = .80-.87), Digit Span (internal consistency = .84-.93; test-retest reliability = .69-.85), Letter Number Sequencing (internal consistency = .75-.88; test-retest reliability = .48-.77) and Spatial Span (internal consistency = .71-.85; test-retest reliability =.65-.69). The Working Memory Index has been shown to be associated with other measures assessing attention. It provides information regarding an individual's ability to attend to verbally presented information, to process that information in memory and then to formulate a response. Standard administration and scoring procedures were used for all the working memory measures as per the WAIS-III and WMS-III manuals. Digit Span consists of single digit numbers presented orally starting with two digits and going to a maximum of nine digits for Digit Span Forward and eight digits for Digit Span Backward. There are two trials for each item, with the test being discontinued after the participant has obtained scores of 0 on both trials for an item. Similarly, for Spatial Span, participants are shown sequences of two up to a maximum of nine for both Spatial Span Forward and Backward. Again, the task is discontinued when responses on both trials of an item are incorrect. For Letter-Number Sequencing, letters and single digits are presented and participants are asked to rearrange the sequence with numbers first in ascending order followed by letters in alphabetical order. There are three trials per item with the test being discontinued when responses on all three trials within an item are incorrect. Length of sequence starts at two and goes up to eight. The Arithmetic task consists of 20 orally presented problems that participants are asked to solve without using paper and pencil. This is the only working memory measure that has a timing component since there are time limits for each mathematical problem. Given that significant practice effects have been observed on the Arithmetic task of the WAIS-R when testing sessions are separated by 2 weeks (Thompson & Sergejew, 1998) and that a change in scaled scores ranging between -3 to +6 was observed following a 2- to 7-week testing interval (Matarazzo & Herman, 1984), an alternate form of this task was used. The alternate form of the Arithmetic task was devised by replacing some of the numbers in the mathematical problems used in the original version for questions five and above given that questions one to four are only administered when questions five or six are not answered correctly as described in the WAIS-III administration procedure. If the test is discontinued after questions 1 to 4 have been administered, practice effects would likely be minimal in a test-retest situation given poor performance. The time limits for each item are the same as for the original task. The alternate numbers and answers are presented in Appendix J.

The Stroop Colour and Word Test was used to assess attention (Hebben & Milberg, 2002). Although previous research in young adults did not show overall improvement on this task following glucose ingestion (Benton et al., 1994; Craft et al., 1994), participants with increasing levels of blood glucose before doing the task performed the interference subtest significantly faster (Benton et al., 1994). The interference trial of this task was also found to be sensitive to improved glycemic control in older adults with type 2 diabetes (Meneilly et al., 1993). Furthermore, some studies have demonstrated that glucose significantly enhances attention (Kaplan et al., 2000; Messier et al., 1997) while others have shown that glucose has no effect on measures of attention (Flint & Turek, 2003; Meikle et al., 2004). The Stroop Colour and Word Test includes three tasks, i.e. word-reading which consists of a page with colour words printed in black ink, colour-naming which includes a page with 'Xs' printed in colour, and colour word-naming which consists of a page with colour words printed in a colour that does not match the word and participants are asked to name the colour of the ink as quickly as possible. Participants have 45 seconds to complete as many items on each section. Research has reported adequate test-retest reliability (word reading = .86, colour naming = .82, colour-word = .73 (Golden, 1975); word reading = .83, colour naming =.74, colour-word = .67 (Franzen, Tishelman, Sharp, & Friedman, 1987)). The interference trial of the Stroop has been associated with tasks assessing attention, inhibition, working memory, speed of processing, conceptual abilities and semantic knowledge (Strauss et al., 2006).

Measures of learning and verbal memory. A modified administration of the Logical Memory subtest of the WMS-III (internal consistency = .71-.90), test-retest reliability = .74-.77) was used since previous research using a similar task had shown the glucose facilitation effect (Craft et al., 1994; Craft et al., 1992; Gonder-Frederick et al., 1987; Hall et al., 1989; Manning et al., 1992; Manning, Stone et al., 1998; Parsons & Gold, 1992). The subtest requires participants to listen to a short story and to recall as much of the story as possible, immediately after presentation (immediate recall) and 25 to 35 minutes later (delayed recall). The two stories had been recorded on an audio cassette and were played for participants instead of having the experimenter read the story at every administration since the rate at which the story is presented has been shown to have an impact on recall, with a higher speed resulting in a lower recall score compared to a slower speed of presentation (Shum, Murray, & Eadie, 1997). One story, either A or B, was used for each visit and the order of presentation of the two stories was counterbalanced across participants. The participant's responses for the two recalls (immediate and delayed) were recorded on an audiotape for scoring purposes. The stories were scored according to the standard criteria as per the WMS-III (Wechsler, 1997b).

The California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 2000) is a word list learning task. The CVLT-II was selected as glucose has been found to enhance performance on a modified version of this task (Foster et al., 1998; Sunram-Lea et al., 2001, 2002a, 2002b, 2004). Participants were presented with 16 words from four categories (List A). There are five trials for List A. A second list was then presented as interference (List B). Participants were then asked to recall List A, first using a free recall format and then using a cued recall format (each category). There is a delayed recall 20 minutes later (free and cued recall) and a recognition trial. The original (internal consistency = .79-.94) and alternate versions (alternate form reliability for the main variables = .72-.79) of the CVLT-II were both used. There are no significant order effects (Delis et al., 2000). Furthermore, the CVLT-II was found to have good concurrent validity with the original CVLT (correlations for the main variables = .72-.80) (Delis et al., 2000). One of the two forms was administered upon each visit and the order of presentation of the forms was counterbalanced across participants. Participants were asked to perform a concomitant task during the five learning trials which consisted of doing two hand motor sequences following the procedure described in Foster et al. (1998), Sunram-Lea et al. (2002b) and Sunram-Lea et al. (2004). This dual-task was chosen as it will allow comparison with previous studies which demonstrated increased memory of words when presented with a concomitant task following glucose ingestion.

Participants were instructed to divide their attention equally on both tasks since research on divided attention has shown that cued recall of a list of word pairs differed according to the instructions given when learning the word pairs while performing a reaction time task (Naveh-Benjamin, Craik, Gavrilescu, & Anderson, 2000). Similarly, free recall of a list of words was also affected by the instructions given when learning the list of words at the same time as completing a reaction time task (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996). Furthermore, research on divided attention has demonstrated that memory performance is minimally affected by divided attention during retrieval while it is substantially reduced when there is division of attention at encoding (Anderson, Craik, & Naveh-Benjamin, 1998; Craik et al., 1996; Craik, Naveh-Benjamin, Ishaik, & Anderson, 2000; Naveh-Benjamin, Craik, Gavrilescu et al., 2000; Naveh-Benjamin, Craik, Guez, & Dori, 1998; Naveh-Benjamin, Craik, Perretta, & Tonev, 2000).

Measure of executive functioning. A modified, computerized version of the Brown-Peterson Task (Brown, 1958; Peterson & Peterson, 1959) was used to assess executive functioning. This Brown-Peterson task was chosen because glucose has been found to improve performance on this task (Martin & Benton, 1999) and older participants with poor glucoregulation obtained significantly lower scores on this task (Messier et al., 2003). Performance on this task involves the recall of auditory information under conditions of interference and has been found to assess divided attention and working memory (Mertens, Gagnon, Coulombe, & Messier, 2006) . Microsoft Office PowerPoint was used for the administration of this task to ensure exact timing of delays. After hearing three consonant letters orally presented by the experimenter (1 second per letter) followed by a 3-digit number, participants were required to immediately begin counting backward from that number by threes until they heard the tone. The shortest and longest delays chosen by Stuss, Stethem and Poirier (1987) were used (delay of 9 seconds and 36 seconds). Upon hearing the tone, participants were asked to recall the three consonants in writing. There were four practice trials per time delay to ensure that participants understood the task. There was a total of 10 testing trials per delay and the order of administration of the delays (Form A: 9-second delay administered first and 36-second delay administered second; Form B: the reverse order) was counterbalanced across participants.

Measure of fine motor skills. Very little research has been conducted on the effect of glucose on motor skills. One study examining the performance of older adults on the Grooved Pegboard following 50 g of glucose did not find any improvements on this task (Allen et al., 1996). However, motor dexterity has been shown to be reduced in older adults with type 2 diabetes (R. Kumar et al., 2008). The Grooved Pegboard is a measure of manual dexterity and visual-motor coordination. It consists of a small board containing 25 holes angled in random directions. Participants have to rotate the pegs to match the holes before placing each peg (Hebben & Milberg, 2002). The Grooved Pegboard task (test–retest reliability = .67-.86) has been shown to be moderately associated to tapping speed, visual acuity, attention, processing speed and non-verbal reasoning (Strauss et al., 2006). Participants were asked to perform a concomitant task with the opposite hand, which consisted of screwing nuts onto bolts that are in a wooden block (see Appendix K). This task was constructed from a piece of wood that was 0.75 inch thick, 12 inches long and 5.5 inches wide. The bolts were 1.75 inches and were placed in rows of five, an inch apart with 1.5 inches between each row. A total of seven rows were included to ensure that participants would not finish this task before completing the Grooved Pegboard. Participants were asked to complete both tasks using their dominant and non-dominant hand. Time required to complete the Grooved Pegboard task (i.e. putting the 25 pegs in the holes) was recorded. An interference task using the same modalities (visuomotor abilities) was chosen as the other dual-task requires different modalities (hearing a word list and performing motor sequences). Furthermore, previous research that examined the impact of ingested glucose on dual tasks only combined tasks that were of different modalities.

Power Analysis

G*Power 3 was used to calculate the number of participants required for this study (Faul, Erdfelder, Lang, & Buchner, 2007). Based on a small to medium effect size (0.35), an alpha of 0.05, power of 0.80, six groups tested on two occasions and an estimated correlation of 0.50 among repeated measures, a total of 90 participants would be required for the between factors, 24 for the within factor and 111 for the within-between interaction. When running the same analysis using a power of 0.90, a sample of 108 participants would be needed for the between factors, 30 for the within factor and 141 for the within-between interaction. Therefore, the aim was to recruit between 100 and 120 participants.

Results

Objectives of the study

The objectives of the study were threefold; examine the impact of three doses of glucose adjusted to body weight on cognitive performance, incorporate dual tasks to test whether glucose facilitation would be more easily observable on tasks requiring dual processing, investigate whether glucoregulation would mediate the glucose facilitation effect on cognitive performance and if age would interact with glucoregulation for this last effect. Therefore, the design included three between-subjects factors (glucose dose, glucoregulation and age) and one within-subjects factor (drinking solution) since age and glucoregulation could not be used as covariates (see below section on potential covariates). Although participants were randomly assigned to one of three doses of glucose, differentiation between better and worse glucoregulators was based on the sample utilized in this study. The order of administration of drinking solutions and test forms (for cognitive measures that included an alternate form) was randomized across participants. Since participants were tested twice within a relatively short test-retest interval (mean number of days between visits = 18.50, *SE* = 1.08), practice effects had to be addressed (see section below). However, the impact of practice effects was reduced by counterbalancing the order of administration of drinking solutions and cognitive measures that had two forms. The statistical software used for all the statistical analyses was SPSS version 16.0 for Windows.

Design

A repeated measures design in which each participant is his or her own control was used as this is typically the design that was used in previous research on glucose and cognition (see review by Riby, 2004), thus controlling for individual differences. Because participants were tested twice using multiple cognitive measures, this constitutes a doubly-multivariate design. An alpha level of 0.05 was used for all statistical analyses.

Sample

A total of 103 participants (age range = 60-85, *M* = 68.22, *SE* = 0.64; education level range = 9-23, *M* = 15.49, *SE* = 0.30), 38 males and 65 females, completed both testing sessions. During the screening interview, 13 people were excluded: 1 for diabetes, 1 for a history of head injury with loss of consciousness lasting more than one hour, 1 for colour-blindness, 1 for chronic hepatitis, 5 because of medication they were currently taking (4 were on antidepressant medication and 1 was on a complex medication regimen) and 4 because of a history of transient ischemic attacks/strokes. Testing was discontinued with six participants (2 males; 4 females), five of which decided not to continue participating in the study either during or after the first visit, and one participant started taking antidepressant medication after the first visit. None of the participants included in the study met exclusionary criteria based on their scores on the BDI-II (range = 0-12; *M* = 2.89, *SE* = 0.30) and the MMSE (range = 26-30; *M* = 28.62, *SE* = 0.10). Only data from participants who completed both testing sessions was analyzed.

Descriptive statistics

Outliers. Standardized scores were examined for age, education, BMI, and exercise to identify univariate outliers (z > 3.29, z < -3.29; Tabachnick & Fidell, 2001). No outliers were observed for age, education and BMI but there was one outlier on the variable exercise (z = 5.04). This case was deleted for subsequent analyses.

Continuous independent variables. Age and glucoregulation were converted into categorical variables since both variables could not be used as covariates (see below section on potential covariates). A median split was used to divide participants in two age groups, younger (60-67 years of age; n = 55) and older (68-85 years of age; n = 49). Since a median split reduces variability and is therefore not ideal, it would have been preferable to divide age in three groups, especially since 65% of participants were between 60 and 69 years of age. However, when dividing participants according to glucose dose received, glucoregulatory group and age group, the total number of participants per cell would have been too small for some groups (i.e. 2 or 4). For glucoregulation, a median split was used for each of the three experimental groups based on glucose dose received to separate the better glucoregulators (lower recover scores; n = 54) and the worse glucoregulators (higher recovery scores; n = 49). The median split was done for each glucose dose group separately since the group receiving the highest dose of glucose (1 g/kg) would have been disproportionately categorized as worse glucoregulators simply because of the higher glucose load.

Risk factors for impaired glucoregulation. Depending on the variable (dichotomous or continuous), chi-square analyses or independent samples t-test were used to compare the glucoregulatory groups on measures of risk factors associated with altered glucoregulation, including body mass index, smoking history, history of diabetes in either parent and frequency of exercise (minutes per week). Apart from body mass index, the other variables were all self-reported by participants. Physical activity could include household chores and manual labour. Glucoregulatory groups did not differ on smoking ($\chi^2(1) = 0.25, p = .62$), BMI ($t(101) = -1.73, p = .09$) or exercise ($t(100) = 0.68, p = .50$). However, there was a significant difference between groups on parental diabetes ($\chi^2(1) = 5.01, p < .03$), with worse regulators having a higher frequency of diabetes in either parent compared to better regulators (better = 6; worse = 14).

Table 2

Frequency or Means (SE) of Risk Factors for Impaired Glucoregulation as a Function of Glucoregulatory Group

Measure	Better glucoregulators	Worse glucoregulators
Smoking (n)	2	1
History of parental diabetes (n)	6	14
Body Mass Index (kg/m^2)	25.86 ± 0.57	27.29 ± 0.60
Exercise (minutes/week)	577.59 ± 51.33	527.55 ± 53.05

Demographic data and premorbid level of intellectual functioning. Demographic data and WTAR standard scores were analyzed using univariate analysis of variance (ANOVA) with glucose dose (300 mg/kg vs. 650 mg/kg vs. 1 g/kg), glucoregulatory group (better vs. worse) and age group (young vs. older) as the between-subject factors. Levene's test of homogeneity of variances was significant for age ($p < .01$) but not for education ($p = .14$) and WTAR ($p = .08$). Therefore, the alpha level was adjusted to 0.025 for the analysis on age to reduce the probability of a Type I error.

Age was not significantly different across glucose groups ($F(2, 91) = 0.09, p = .91$) or glucoregulatory groups ($F(1, 91) = 0.57, p = .45$), and the interaction was not significant ($F(2, 91) = 0.05, p = .96$). However, there was a significant difference in age between both age groups ($F(1, 91) = 163.56, p < .01$; younger group: $M = 63.36$, $SE = 0.56$; older group: $M = 73.73$, $SE = 0.59$), indicating that the median split on this continuous variable distinguished the two groups. None of the interactions were significant (age and glucose dose: $F(2, 91) = 0.22, p = .80$; age and glucoregulation: $F(1, 91) = 1.34, p = .25$; age, glucose dose and glucoregulation: $F(2, 91) = 0.37, p = .70$). Since there was a violation of the assumption of homogeneity of variances and the group sizes were unequal, Welch's test of equality of means was also computed to further ensure that both age groups differed on age. This analysis led to the same conclusion ($F(1, 64.16) = 168.85, p < .01$).

Level of education was also comparable across glucose groups ($F(2, 91) = 0.28, p = .76$) and glucoregulatory groups ($F(1, 91) = 1.80, p = .18$), and the interaction was not significant ($F(2, 91) = 0.85, p = .43$). There was a significant difference between both age groups on level of education ($F(1, 91) = 11.88, p < .01$), with the younger group ($M = 16.33$, $SE = 0.41$) having a higher level of education compared to the older group ($M = 14.31$, $SE = 0.43$). None of the interactions were significant (age and glucose dose: $F(2, 91) = 0.27, p =$

.77; age and glucoregulation: $F(1, 91) = 1.94, p = .17$; age, glucose dose and glucoregulation: $F(2, 91) = 2.13, p = .13$).

Estimated premorbid level of intellectual functioning, as assessed by the WTAR, was comparable across glucose groups ($F(2, 91) = 0.20, p = .82$), glucoregulatory groups ($F(1, 91) = 0.53, p = .47$) and age groups ($F(1, 91) = 0.01, p = .91$). All the interactions between variables were not significant (glucose dose and glucoregulation: $F(2, 91) = 0.16, p = .85$; age and glucose dose: $F(2, 91) = 0.07, p = .93$; age and glucoregulation: $F(1, 91) = 0.42, p = .52$; age, glucose dose and glucoregulation: $F(2, 91) = 0.76, p = .47$). Although age groups differed on level of education (a typical finding for these age cohorts), both groups had similar standard scores on the WTAR, indicating that they had comparable estimated intellectual functioning at the start of the experiment. Furthermore, WTAR standard scores correlated more highly with the cognitive measures than level of education (see correlations below), suggesting that performance on the WTAR is more relevant than level of education.

Blindness to solution ingested. Participants were asked to indicate which solution they thought they had received during the second visit to ensure that they were blind to solution ingested. Chi-square analysis was non-significant ($\chi^2(1) = 0.59, p = .44$) indicating that identification of solution was not significantly different from chance.

From these analyses, we can conclude that observed changes associated with treatments were not due to between groups pre-existing differences (with the exception of age and glucoregulation) between the experimental groups.

Blood glucose levels

Outliers. Standardized scores were examined for all blood glucose variables to determine whether there were any univariate outliers ($z > 3.29$, $z < -3.29$; Tabachnick & Fidell, 2001). A total of 6 cases were identified as outliers. Since blood glucose levels were repeated measures, the value for each outlier was replaced with the group mean (see Table 3).

Table 3

Univariate Outliers on the Blood Glucose Measurements that were Replaced with the Group Mean

Measure	Case #	z value	Group	Group mean
		Saccharin solution		
Fasting	7	6.48	older, 1 g/kg, worse	5.4
30 min	7	6.06	older, 1 g/kg, worse	5.3
120 min	7	5.57	older, 1 g/kg, worse	5.2
		Glucose solution		
Fasting	7	3.45	older, 1 g/kg, worse	5.3
120 min	7	3.79	older, 1 g/kg, worse	10.4
120 min	49	4.53	older, 1 g/kg, worse	10.4

Blood glucose levels were analyzed using a split-plot repeated measures ANOVA with glucose dose (300 mg/kg vs. 650 mg/kg vs. 1 g/kg), glucoregulatory group (better vs. worse) and age group (young vs. older) as the between-subject factors and time of blood glucose measures (baseline, 30 minutes and 2-hour) and solution (glucose or saccharin) as the within-subject variables. The analysis was run both on the original data and on the modified data (outliers replaced with the group mean). Since some of the effects that were significant in the analysis that was run on the original data were no longer significant in the analysis on the modified data, the latter analysis was retained. Since the assumption of sphericity was not met ($p < .01$) for time and the interaction between time and solution, Greenhouse-Geisser correction was used. There was a significant main effect of time ($F(1.69, 153.73) = 400.52, p < .01$) and solution ($F(1, 91) = 634.21, p < .01$). Several two-way interactions were significant: time and glucose dose ($F(3.38, 153.73) = 12.35, p < .01$), time and glucoregulation ($F(1.69, 153.73) = 53.23, p < .01$), solution and glucose dose ($F(2, 91) = 17.02, p < .01$), solution and glucoregulation ($F(1, 91) = 34.20, p < .01$) as well as time and solution ($F(1.66, 151.46) = 404.51, p < .01$). However, these results were further explained by a three-way interaction between time, solution and glucose dose ($F(3.33, 151.46) = 9.55, p < .01$) and a three-way interaction between time, solution and glucoregulation ($F(1.66, 151.46) = 46.26, p < .01$). Figure 1 shows the interaction between time, solution and glucose dose. Bonferroni planned comparisons revealed that there was a significant difference between the blood glucose measurement 30 minutes following glucose ingestion compared to measurements taken at baseline and 120 minutes after drinking the glucose solution for the 300 mg/kg group (baseline: $M = 5.33$, $SE = 0.10$; 30 min: $M = 8.66$, $SE = 0.29$; 120 min: $M = 5.50$, $SE = 0.19$), the 650 mg/kg group (baseline: $M = 5.43$, $SE = 0.10$; 30 min: $M = 9.31$, $SE = 0.28$; 120 min: $M = 6.70$, $SE = 0.18$) and the 1 g/kg group (baseline: *M* = 5.23, *SE* = 0.10; 30 min: *M* = 9.46, *SE* = 0.29; 120 min: *M* = 7.62, *SE* = 0.18). Furthermore, there was a significant difference between the baseline and 120 min measurement in the 650 mg/kg group and the 1 g/kg group but not in the 300 mg/kg group. No significant differences were observed in the saccharin condition. These results show that the higher doses led to higher peak blood glucose levels at 30 min and resulted in a slower return to baseline glucose levels.

As for the interaction between glucoregulation, time and solution (see Figure 2), there was a significant difference between better regulators and worse regulators at the 120 min measurement in the glucose condition, with better regulators having significantly lower blood glucose levels (*M* = 5.36, *SE* = 0.15) compared to worse regulators (*M* = 7.86, *SE* = 0.15). There were no significant differences in blood glucose measurements between glucoregulatory groups in the saccharin condition. These analyses show that the participants categorized as having worse glucoregulation showed the slow return to baseline following glucose ingestion that is typical of impaired glucose tolerance.

Figure 1. Blood glucose levels as a function of time of measurement, solution and glucose dose.

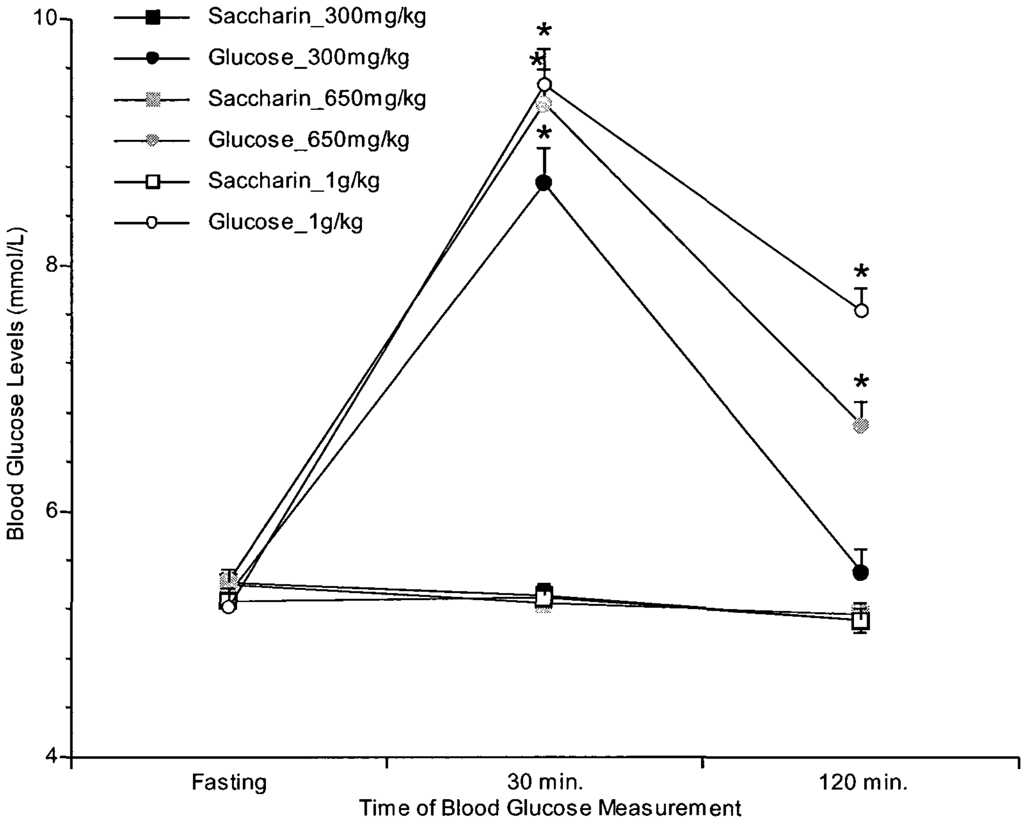
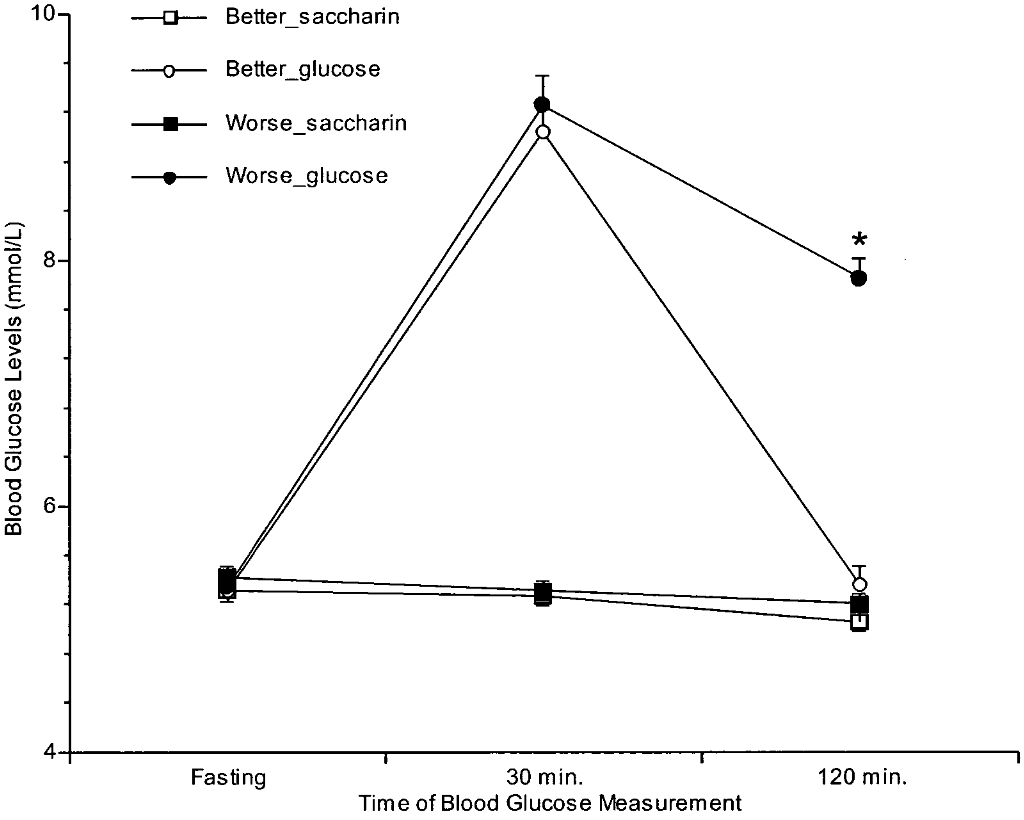


Figure 2. Blood glucose levels as a function of time of measurement, solution and glucoregulation.



Cognitive measures

Equivalency of alternate forms. Alternate forms were used for the two verbal memory measures, the CVLT-II and the Logical Memory subtest of the WMS-III, as well as the Arithmetic subtest of the WAIS-III. To ensure that alternate forms were comparable, data from the first visit was analyzed using independent samples t-test to compare both forms for each of these three cognitive measures. A total of 52 participants received the original form of each task during the first visit compared to 51 participants who were administered the alternate form. There were no significant differences between scores on both forms of the Arithmetic subtest ($t(101) = -0.80, p = .42$). For the Logical Memory task, analyses were conducted separately for the immediate and delayed recalls. Recall for the stories did not differ significantly, in the immediate ($t(101) = 1.89, p = .06$) or delayed recall condition ($t(101) = 0.85, p = .40$). The original and alternate versions of the CVLT-II were also found to be comparable on all recall scores: total immediate free recall ($t(101) = 1.48, p = .14$), free recall of interference list ($t(101) = -0.10, p = .92$), short-delay free recall ($t(101) = 1.10, p = .28$), short-delay cued recall ($t(85.51) = 1.56, p = .12$), long-delay free recall ($t(94.56) = 1.56, p = .12$), long-delay cued recall ($t(97.79) = 1.54, p = .13$) and long-delay recognition hits ($t(101) = 0.63, p = .53$).

Neuropsychological variables. A total of 9 cognitive measures were administered, resulting in a total of 33 scores. Initially, principal component factor analysis was run separately for saccharin and glucose to reduce the number of cognitive variables. However, the result obtained was not the same for both drinking solutions. Therefore, an attempt was made to reduce the amount of dependent variables by only using variables that were the most representative of each measure. Furthermore, variables that were highly correlated within a cognitive measure ($r \geq .70$) were combined (Tabachnick & Fidell, 2001). Correlations were computed separately for saccharin and glucose solutions. Finally, for cognitive measures that included both separate and total scores, only one of those options was retained to avoid singularity.

Several variables were combined because of high intercorrelations. For the CVLT-II, the short-delay free and cued recall scores as well as the long-delay free and cued recall scores were all highly correlated (see Table 4) and were therefore combined into one variable representing the CVLT-II total delayed recall. The immediate and delayed recall scores of the Logical Memory were also highly correlated ($r = .88$ for saccharin solution; $r = .94$ for glucose solution) and were combined in a total recall score. Finally, both scores obtained on the Grooved Pegboard, the total time to complete the task with the dominant hand and the non-dominant hand, were also highly related ($r = .83$ for saccharin solution; $r = .81$ for glucose solution) and therefore combined in one total score for that measure.

Table 4

Correlations Between CVLT-II Delayed Recall Scores

CVLT-II measure	Short-delay free recall	Short-delay cued recall	Long-delay free recall	Long-delay cued recall
	Saccharin solution			
Short-delay free recall	—	.88**	.88**	.85**
Short-delay cued recall		—	.91**	.92**
Long-delay free recall			—	.93**
Long-delay cued recall				—
	Glucose solution			
Short-delay free recall	—	.83**	.82**	.80**
Short-delay cued recall		—	.86**	.90**
Long-delay free recall			—	.92**
Long-delay cued recall				—

Note. CVLT-II = California Verbal Learning Test-Second Edition; $^{**}p < .01$

The CVLT-II includes both individual scores for each of the five learning trials and a total immediate free recall score. The total score was chosen to reflect learning of the list of words. As for the Spatial Span and Digit Span, scores were kept separate for forward and backward since Digit Span Forward assesses efficiency of attention while Digit Span Backward measures working memory (Lezak, Howieson, & Loring, 2004), and to be able to compare simple and more complex visual and auditory attention. The total number of neuropsychological variables was therefore reduced to 19 variables.

Outliers. Standardized scores were examined for all cognitive variables to determine the presence of univariate outliers ($z > 3.29$, $z < -3.29$; Tabachnick & Fidell, 2001) and Mahalanobis distance was used to identify multivariate outliers. Although there were no multivariate outliers (no cases with a value greater than $\chi^2(38) = 70.67$), a total of 18 cases were identified as univariate outliers. Since a repeated measures design was used, the value for each outlier was replaced with the group mean (age group, glucoregulatory group and glucose dose received) for that particular participant (see Table 5). Deleting those cases would have resulted in the loss of 9 participants. The analysis on impact of drinking solution, glucose dose, glucoregulation and age on cognitive performance was run both with the outliers and the outliers replaced with the group mean (see results below).

Table 5

Univariate Outliers on the Cognitive Measures that were Replaced with the Group Mean

Cognitive measure	Case #	z value	Group	Group mean
		Saccharin solution		
CVLT-II FP	94	3.52	younger, 300 mg/kg, better	5
CVLT-II Intru	27	4.83	older, 300 mg/kg, worse	7
Grooved Peg	7	3.47	older, 1 g/kg, worse	166.0
Grooved Peg	98	4.31	older, 650 mg/kg, worse	179.0
MBPT 9	98	-3.54	older, 650 mg/kg, worse	20
LNS	12	3.55	younger, 650 mg/kg, worse	9
Stroop W	98	-3.67	older, 650 mg/kg, worse	90
Stroop C	98	-3.65	older, 650 mg/kg, worse	64
Stroop CW	48	4.08	older, 300 mg/kg, worse	32
		Glucose solution		
CVLT-II Imm	39	3.45	younger, 300 mg/kg, better	34
CVLT-II Inte	35	3.42	younger, 1 g/kg, worse	5
CVLT-II FP	27	3.95	older, 300 mg/kg, worse	6
CVLT-II Intru	27	4.98	older, 300 mg/kg, worse	11
CVLT-II Intru	65	4.34	older, 300 mg/kg, better	10
SSpan Fwd	39	3.31	younger, 300mg/kg, better	8
Grooved Peg	98	3.72	older, 650 mg/kg, worse	170.5
MBPT 9	98	-3.46	older, 650 mg/kg, worse	17
Stroop CW	48	3.59	older, 300 mg/kg, worse	32

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Practice effects. To examine the presence of practice effects from the first testing session to the second testing session, a doubly-multivariate analysis was conducted with the within-subject factor of session (first or second). Sphericity was not an issue since the repeated measure (session) had only two levels. The Wilks' Lambda multivariate test was significant ($F(19, 84) = 5.36, p < .01$). Univariate tests revealed practice effects on 11 out of the 19 cognitive variables: CVLT-II Total Immediate Free Recall ($F(1, 102) = 18.16, p < .01$), CVLT-II Short and Long-Delay Free and Cued Recall ($F(1, 102) = 4.46, p < .04$), CVLT-II Long-Delay Recognition Hits ($F(1, 102) = 5.68, p < .02$), CVLT-II Long-Delay Recognition False-Positives ($F(1, 102) = 5.06, p < .03$), Grooved Pegboard Total ($F(1, 102) = 11.83, p < .01$), Modified Brown-Peterson Task 9 seconds ($F(1, 102) = 6.46, p < .02$), Modified Brown-Peterson Task 36 seconds ($F(1, 102) = 4.09, p < .05$), Logical Memory Immediate and Delayed Recall ($F(1, 102) = 25.25, p < .01$), Digit Span Backward ($F(1, 102) = 5.05, p < .03$), Stroop Colour ($F(1, 102) = 5.32, p < .03$), and Stroop Colour-Word ($F(1, 102) = 20.14, p < .01$). Means are presented in Table 6.

Practice effects on measures with alternate forms were also examined separately for each order of administration. The Wilks' Lambda multivariate test was non-significant ($F(8, 44) = 1.99, p = .07$) when the original form was administered first and the alternate form given on the second visit. However, Wilks' Lambda multivariate test was significant when the alternate form was used during the first session and the original form was administered during the subsequent session ($F(8, 43) = 18.66, p < .01$). Univariate tests revealed significant results on 4 out of the 8 measures: CVLT-II Total Immediate Free Recall ($F(1, 50) = 24.80, p < .01$; session 1: $M = 31.78$, $SE = 1.16$; session 2: $M = 37.41$, $SE = 1.35$), CVLT-II Short and Long-Delay Free and Cued Recall ($F(1, 50) = 8.03, p < .01$; session 1: $M = 7.48$, $SE = 0.42$; session 2: $M = 8.28$, $SE = 0.41$), CVLT-II Long-Delay Recognition Hits

($F(1, 50) = 8.47, p < .01$; session 1: $M = 12.65$, $SE = 0.30$; session 2: $M = 13.51$, $SE = 0.31$) and Logical Memory Immediate and Delayed Recall ($F(1, 50) = 93.95, p < .01$; session 1: $M = 11.06$, $SE = 0.46$; session 2: $M = 15.43$, $SE = 0.47$).

Although significant practice effects and order effects are observed on several cognitive measures, the order of administration of the drinking solutions and of the original/alternate forms followed a counterbalanced sequence. However, this raises the possibility (addressed later) that practice effects increased data variability and may have contributed to mask significant effects.

Table 6

Performance on each Cognitive Measure (means ± standard error) during the First Visit and the Second Visit

Measure	First visit	Second visit
CVLT-II Total Immediate Free Recall	32.95 ± 0 .79	36.71 ± 0.92**
CVLT-II Free Recall of Interference List	5.00 ± 0.18	5.08 ± 0.18
CVLT-II Short and Long-Delay Free and Cued Recall	7.88 ± 0.26	8.38 ± 0.29*
CVLT-II Long-Delay Recognition Hits	12.78 ± 0.20	13.29 ± 0.21*
CVLT-II Long-Delay Recognition False-Positives[a]	5.69 ± 0.47	6.67 ± 0.49*
CVLT-II Total Intrusions[a]	5.95 ± 0.58	7.37 ± 0.67
Spatial Span Forward	8.18 ± 0.15	8.15 ± 0.16
Spatial Span Backward	7.18 ± 0.17	7.35 ± 0.16
Grooved Pegboard Total[a]	160.23 ± 4.16	151.73 ± 3.94**
Modified Brown-Peterson Task 9 seconds	21.29 ± 0.55	22.48 ± 0.52*
Modified Brown-Peterson Task 36 seconds	20.11 ± 0.66	21.07 ± 0.70*
Logical Memory Immediate and Delayed Recall	11.55 ± 0.35	13.64 ± 0.39**
Arithmetic	14.93 ± 0.33	15.25 ± 0.33
Digit Span Forward	9.99 ± 0.22	10.20 ± 0.23
Digit Span Backward	7.16 ± 0.22	7.53 ± 0.23*
Letter-Number Sequencing	9.53 ± 0.21	9.85 ± 0.21
Stroop Word	95.61 ± 1.28	94.12 ± 1.46
Stroop Colour	64.36 ± 1.00	65.83 ± 1.11*
Stroop Colour-Word	34.81 ± 0.77	37.23 ± 0.82**

Note. CVLT-II = California Verbal Learning Test-Second Edition; [a]Lower score = Better performance; $*p < .05$; $**p < .01$.

Potential covariates. Correlations were computed between age, education, WTAR score and all dependent variables (separately for saccharin and glucose) to determine whether these variables should be used as covariates in subsequent analyses (see Table 7). Of these three variables, WTAR scores was the variable that appeared the most associated with the cognitive measures (higher number of stronger correlations). However, there were not enough moderate correlations to justify using WTAR as a covariate.

Since one of the objectives of this study was to examine whether age would interact with glucoregulation to influence cognitive performance, the analysis examining the impact of drinking solution, glucose dose and glucoregulation on cognitive performance (doubly-multivariate analysis) was conducted with age as a covariate. However, there was a significant interaction between the within-subject factor (solution) and the covariate age ($F(19, 78) = 1.80, p < .04$), indicating that there is a violation of the homogeneity of the slopes assumption. Hence, age could not be used as a covariate.

Correlations were also computed between recovery index and the cognitive variables (separately for saccharin and glucose) to examine whether this continuous variable could be used as a covariate (see Table 8). Recovery scores were converted into z scores by using the mean and the standard deviation of the corresponding glucose dose group. Both overall correlations and correlations between recovery index z scores and cognitive measures presented separately according to glucose dose received were low. Therefore, recovery index could not be used as a covariate.

Table 7

Correlations between Age, Education and WTAR Score and Performance on Cognitive Variables following the Saccharin Solution and the Glucose Solution

Cognitive variables	Age	Education	WTAR
Saccharin solution			
CVLT-II Total Immediate Free Recall	-.31**	.13	-.01
CVLT-II Free Recall of Interference List	-.27**	.10	.25*
CVLT-II Short and Long-Delay Free and Cued Recall	-.33**	.13	.08
CVLT-II Long-Delay Recognition Hits	-.40**	-.06	-.15
CVLT-II Long-Delay Recognition False-Positives	.11	-.25**	-.09
CVLT-II Total Intrusions	.10	-.20*	-.27**
Spatial Span Forward	-.27**	.02	.06
Spatial Span Backward	-.03	.26**	.28**
Grooved Pegboard Total	.43**	-.10	.02
Modified Brown-Peterson Task 9 seconds	-.28**	.13	.28**
Modified Brown-Peterson Task 36 seconds	-.28**	.14	.19
Logical Memory Immediate and Delayed Recall	-.35**	.09	.10
Arithmetic	-.21*	.40**	.33**
Digit Span Forward	-.03	.04	.30**
Digit Span Backward	-.09	.15	.46**
Letter-Number Sequencing	-.21*	.12	.38**
Stroop Word	-.18	.15	.25*
Stroop Colour	-.23*	.08	.04
Stroop Colour-Word	-.36**	.23*	.06
Glucose solution			
CVLT-II Total Immediate Free Recall	-.28**	.17	.17
CVLT-II Free Recall of Interference List	-.34**	.09	.09
CVLT-II Short and Long-Delay Free and Cued Recall	-.25**	.14	.18
CVLT-II Long-Delay Recognition Hits	-.16	-.07	-.02
CVLT-II Long-Delay Recognition False-Positives	.04	-.27**	-.19
CVLT-II Total Intrusions	.21*	-.25*	-.17
Spatial Span Forward	-.17	.16	.13
Spatial Span Backward	-.29**	.20*	.21*
Grooved Pegboard Total	.47**	-.20*	-.06
Modified Brown-Peterson Task 9 seconds	-.25*	.15	.20*
Modified Brown-Peterson Task 36 seconds	-.26**	.17	.26**
Logical Memory Immediate and Delayed Recall	-.04	.24*	.43**
Arithmetic	-.19	.34**	.44**
Digit Span Forward	-.04	.12	.37**
Digit Span Backward	-.14	.12	.41**
Letter-Number Sequencing	-.23*	.13	.44**
Stroop Word	-.20*	.18	.29**
Stroop Colour	-.25*	.09	.12
Stroop Colour-Word	-.38**	.25*	.05

Note. CVLT-II = California Verbal Learning Test-Second Edition; **p* < .05; ***p* < .01

Table 8

Correlations between Recovery Index Standardized Scores and Performance on Cognitive Variables following the ingestion of Saccharin or Glucose

Cognitive variables	Overall	300 mg/kg	650 mg/kg	1 g/kg
Saccharin solution				
CVLT-II Total Immediate Free Recall	-.14	.05	.03	-.32
CVLT-II Free Recall of Interference List	-.13	-.19	-.33	.00
CVLT-II Short and Long-Delay Free and Cued Recall	-.07	.05	.05	-.22
CVLT-II Long-Delay Recognition Hits	-.01	.08	.07	-.16
CVLT-II Long-Delay Recognition False-Positives	.00	-.05	-.13	.08
CVLT-II Total Intrusions	-.15	-.12	-.10	-.06
Spatial Span Forward	-.01	.16	-.07	-.13
Spatial Span Backward	.11	.29	.01	.07
Grooved Pegboard Total	.02	.12	.10	.08
Modified Brown-Peterson Task 9 seconds	.00	.10	.00	-.03
Modified Brown-Peterson Task 36 seconds	-.03	.23	-.10	-.08
Logical Memory Immediate and Delayed Recall	-.02	.06	-.17	-.02
Arithmetic	-.15	.09	-.20	-.15
Digit Span Forward	.12	.17	.27	.07
Digit Span Backward	-.17	.21	-.21	-.26
Letter-Number Sequencing	-.14	.16	-.08	-.33
Stroop Word	-.06	.08	-.09	-.07
Stroop Colour	-.11	-.02	-.21	.04
Stroop Colour-Word	-.04	-.16	-.03	-.13
Glucose solution				
CVLT-II Total Immediate Free Recall	.02	.34	-.03	-.20
CVLT-II Free Recall of Interference List	-.14	.07	-.36	-.18
CVLT-II Short and Long-Delay Free and Cued Recall	.02	.21	.10	-.12
CVLT-II Long-Delay Recognition Hits	.02	-.09	-.11	.13
CVLT-II Long-Delay Recognition False-Positives	-.04	-.14	-.22	.06
CVLT-II Total Intrusions	-.07	-.04	.01	-.09
Spatial Span Forward	.06	.31	.08	.00
Spatial Span Backward	.12	.02	.28	.08
Grooved Pegboard Total	.12	.22	-.08	.25
Modified Brown-Peterson Task 9 seconds	-.21*	.10	-.27	-.39*
Modified Brown-Peterson Task 36 seconds	-.11	.19	-.14	-.24
Logical Memory Immediate and Delayed Recall	-.02	.27	-.10	-.13
Arithmetic	-.07	.24	-.20	-.14
Digit Span Forward	.07	.03	-.01	.26
Digit Span Backward	-.17	.16	-.20	-.23
Letter-Number Sequencing	-.11	.09	.00	-.23
Stroop Word	-.15	-.04	-.28	-.11
Stroop Colour	-.09	-.07	-.08	-.04
Stroop Colour-Word	-.11	-.17	-.11	-.15

Note. CVLT-II = California Verbal Learning Test-Second Edition; *$p < .05$; **$p < .01$

Impact of drinking solution, glucose dose, glucoregulation and age on cognitive performance

To examine the impact of solution, glucose dose, glucoregulation and age on cognition, a doubly-multivariate analysis was conducted with the between-subject factors of glucose dose (300 mg/kg vs. 650 mg/kg vs. 1 g/kg), glucoregulation (better vs. worse) and age (younger vs. older) and the within-subject factor of solution (glucose or saccharin). Means are presented in Table 9 for younger participants and in Table 10 for older participants.

Levene's test of equality of error variances was only significant for one variable, CVLT-II total intrusions (glucose solution), $p < .03$. Therefore, the alpha level was adjusted to .025 for that variable. Sphericity was not an issue since the repeated measure (solution) had only two levels. The multivariate analysis revealed non-significant results apart from an overall significant effect of age group (see Table 11). However, significant results from the univariate analyses will be presented as they can offer possible insights for future research (Tabachnick & Fidell, 2001). When a significant interaction was found, this interaction was plotted in a figure to help visualize the data.

Table 9

Cognitive Performance (means ± standard error) of Younger Participants as a Function of Glucose Dose, Glucoregulation and Drinking Solution

	300 mg/kg		650 mg/kg		1 g/kg	
	Better (n = 9)	Worse (n =5)	Better (n = 11)	Worse (n = 9)	Better (n = 12)	Worse (n = 9)
			Saccharin solution			
CVLT-II Imm	38.33 ± 2.99	37.40 ± 4.02	36.55 ± 2.71	35.78 ± 2.99	34.75 ± 2.59	35.33 ± 2.99
CVLT-II Inte	5.56 ± 0.58	4.80 ± 0.78	5.82 ± 0.52	4.78 ± 0.58	4.92 ± 0.50	5.56 ± 0.58
CVLT-II Del	9.28 ± 0.99	9.85 ± 1.33	9.21 ± 0.89	8.25 ± 0.99	8.42 ± 0.86	8.17 ± 0.99
CVLT-II Hits	13.89 ± 0.67	13.60 ± 0.90	13.09 ± 0.60	13.56 ± 0.67	13.50 ± 0.58	13.33 ± 0.67
CVLT-II FP	4.89 ± 1.64	4.40 ± 2.20	4.27 ± 1.48	6.89 ± 1.64	6.25 ± 1.42	7.67 ± 1.64
CVLT-II Intru	8.00 ± 1.89	6.20 ± 2.53	7.64 ± 1.71	7.67 ± 1.89	4.83 ± 1.64	3.56 ± 1.89
SSpan Fwd	7.78 ± 0.51	8.60 ± 0.68	8.09 ± 0.46	8.56 ± 0.51	8.83 ± 0.44	8.78 ± 0.51
SSpan Bwd	7.33 ± 0.56	7.20 ± 0.75	7.36 ± 0.51	6.89 ± 0.56	7.75 ± 0.49	8.00 ± 0.56
Grooved Peg	140.89 ± 11.39	112.90 ± 15.27	147.55 ± 10.30	153.61 ± 11.39	134.38 ± 9.86	134.11 ± 11.39
MBPT 9	23.67 ± 1.85	23.80 ± 2.49	20.00 ± 1.68	23.56 ± 1.85	22.58 ± 1.60	22.67 ± 1.85
MBPT 36	21.78 ± 2.23	23.60 ± 2.99	21.73 ± 2.02	23.56 ± 2.23	20.83 ± 1.93	21.00 ± 2.23
LM Recall	12.56 ± 1.13	15.60 ± 1.51	14.36 ± 1.02	13.44 ± 1.13	13.58 ± 0.97	12.39 ± 1.13
Arithmetic	16.78 ± 1.10	15.80 ± 1.48	16.09 ± 1.00	15.00 ± 1.10	15.75 ± 0.95	15.56 ± 1.10
DSpan Fwd	10.78 ± 0.70	9.80 ± 0.94	9.55 ± 0.64	9.56 ± 0.70	10.17 ± 0.61	11.00 ± 0.70
DSpan Bwd	8.33 ± 0.77	7.80 ± 1.03	7.27 ± 0.69	6.89 ± 0.77	7.25 ± 0.66	7.89 ± 0.77
LNS	10.00 ± 0.62	10.40 ± 0.84	8.64 ± 0.56	9.22 ± 0.62	10.33 ± 0.54	10.44 ± 0.62
Stroop W	101.22 ± 4.29	99.20 ± 5.76	95.82 ± 3.88	94.89 ± 4.29	93.75 ± 3.72	91.89 ± 4.29
Stroop C	69.11 ± 3.25	74.20 ± 4.36	68.36 ± 2.94	62.67 ± 3.25	63.17 ± 2.81	63.44 ± 3.25
Stroop CW	37.22 ± 2.55	38.00 ± 3.41	38.55 ± 2.30	37.33 ± 2.55	39.42 ± 2.20	38.44 ± 2.55
			Glucose solution			
CVLT-II Imm	33.89 ± 2.87	37.60 ± 3.85	37.82 ± 2.60	30.89 ± 2.87	39.42 ± 2.48	35.22 ± 2.87
CVLT-II Inte	5.22 ± 0.61	6.00 ± 0.82	5.73 ± 0.56	4.33 ± 0.61	5.92 ± 0.53	4.89 ± 0.61
CVLT-II Del	8.56 ± 0.94	9.65 ± 1.26	8.91 ± 0.85	7.39 ± 0.94	9.21 ± 0.81	7.56 ± 0.94
CVLT-II Hits	13.67 ± 0.74	12.40 ± 1.00	13.18 ± 0.67	12.67 ± 0.74	13.08 ± 0.64	13.56 ± 0.74
CVLT-II FP	4.56 ± 1.65	5.40 ± 2.21	4.27 ± 1.49	6.11 ± 1.65	6.00 ± 1.43	7.89 ± 1.65
CVLT-II Intru	4.22 ± 2.35	4.60 ± 3.16	6.55 ± 2.13	4.56 ± 2.35	4.50 ± 2.04	6.89 ± 2.35
SSpan Fwd	7.78 ± 0.52	10.20 ± 0.70	7.27 ± 0.47	8.00 ± 0.52	8.67 ± 0.45	8.67 ± 0.52
SSpan Bwd	7.56 ± 0.53	8.00 ± 0.71	7.09 ± 0.48	8.22 ± 0.53	7.42 ± 0.46	7.89 ± 0.53
Grooved Peg	141.67 ± 12.90	122.80 ± 17.30	150.73 ± 11.66	142.83 ± 12.90	129.25 ± 11.17	143.33 ± 12.90
MBPT 9	23.11 ± 1.74	23.20 ± 2.34	22.09 ± 1.58	21.89 ± 1.74	24.92 ± 1.51	21.00 ± 1.74
MBPT 36	23.22 ± 2.31	24.20 ± 3.10	19.00 ± 2.09	20.78 ± 2.31	22.58 ± 2.00	21.33 ± 2.31
LM Recall	13.22 ± 1.45	12.60 ± 1.94	12.05 ± 1.31	11.61 ± 1.45	12.79 ± 1.25	11.28 ± 1.45
Arithmetic	16.11 ± 1.09	14.80 ± 1.46	15.64 ± 0.98	14.56 ± 1.09	16.25 ± 0.94	15.22 ± 1.09
DSpan Fwd	10.56 ± 0.76	10.00 ± 1.02	9.36 ± 0.69	9.67 ± 0.76	9.67 ± 0.66	11.33 ± 0.76
DSpan Bwd	8.78 ± 0.75	7.80 ± 1.00	8.00 ± 0.68	7.22 ± 0.75	6.75 ± 0.65	7.78 ± 0.75
LNS	10.67 ± 0.76	9.60 ± 1.03	9.64 ± 0.69	10.22 ± 0.76	10.42 ± 0.66	10.00 ± 0.76
Stroop W	102.67 ± 5.16	97.80 ± 6.92	100.00 ± 4.67	89.89 ± 5.16	95.50 ± 4.47	95.56 ± 5.16
Stroop C	69.78 ± 3.96	70.80 ± 5.31	64.36 ± 3.58	64.78 ± 3.96	65.42 ± 3.43	64.44 ± 3.96
Stroop CW	39.22 ± 2.73	39.80 ± 3.67	40.00 ± 2.47	33.22 ± 2.73	40.17 ± 2.37	38.56 ± 2.73

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Table 10

Cognitive Performance (means ± standard error) of Older Participants as a Function of Glucose Dose, Glucoregulation and Drinking Solution

	300 mg/kg		650 mg/kg		1 g/kg	
	Better (n = 9)	Worse (n =11)	Better (n = 7)	Worse (n = 8)	Better (n = 6)	Worse (n = 7)
			Saccharin solution			
CVLT-II Imm	34.11 ± 2.99	33.36 ± 2.71	33.71 ± 3.40	36.50 ± 3.18	38.00 ± 3.67	25.14 ± 3.40
CVLT-II Inte	4.22 ± 0.58	4.55 ± 0.52	5.43 ± 0.66	4.38 ± 0.61	4.50 ± 0.71	4.14 ± 0.66
CVLT-II Del	7.11 ± 0.99	7.52 ± 0.89	7.68 ± 1.12	8.91 ± 1.05	8.50 ± 1.21	5.86 ± 1.12
CVLT-II Hits	12.00 ± 0.67	12.36 ± 0.60	13.00 ± 0.76	13.13 ± 0.71	13.33 ± 0.82	11.57 ± 0.76
CVLT-II FP	8.56 ± 1.64	8.00 ± 1.48	7.00 ± 1.86	5.25 ± 1.74	5.17 ± 2.01	8.57 ± 1.86
CVLT-II Intru	9.33 ± 1.89	7.09 ± 1.71	8.86 ± 2.14	3.88 ± 2.00	6.00 ± 2.31	5.29 ± 2.14
SSpan Fwd	8.44 ± 0.51	7.91 ± 0.46	8.57 ± 0.57	7.13 ± 0.54	8.17 ± 0.62	7.71 ± 0.57
SSpan Bwd	7.00 ± 0.56	7.73 ± 0.51	6.71 ± 0.63	7.25 ± 0.59	6.67 ± 0.69	7.29 ± 0.63
Grooved Peg	161.33 ± 11.39	188.82 ± 10.30	174.57 ± 12.91	178.94 ± 12.08	145.17 ± 13.94	166.14 ± 12.91
MBPT 9	21.22 ± 1.85	21.64 ± 1.68	21.71 ± 2.10	19.63 ± 1.96	23.00 ± 2.27	19.00 ± 2.10
MBPT 36	17.67 ± 2.23	22.09 ± 2.02	20.29 ± 2.53	15.88 ± 2.37	24.17 ± 2.73	17.00 ± 2.53
LM Recall	11.44 ± 1.13	11.73 ± 1.02	13.29 ± 1.28	12.25 ± 1.19	14.75 ± 1.38	12.21 ± 1.28
Arithmetic	14.67 ± 1.10	16.09 ± 1.00	15.14 ± 1.25	12.75 ± 1.17	14.17 ± 1.35	12.57 ± 1.25
DSpan Fwd	10.33 ± 0.70	11.73 ± 0.64	8.14 ± 0.80	9.88 ± 0.75	9.83 ± 0.86	9.86 ± 0.80
DSpan Bwd	7.44 ± 0.77	8.46 ± 0.69	7.43 ± 0.87	6.25 ± 0.81	6.83 ± 0.94	6.14 ± 0.87
LNS	8.78 ± 0.62	10.55 ± 0.56	9.43 ± 0.71	8.75 ± 0.66	9.33 ± 0.76	7.86 ± 0.71
Stroop W	91.89 ± 4.29	95.09 ± 3.88	92.86 ± 4.86	90.25 ± 4.55	95.50 ± 5.25	93.86 ± 4.86
Stroop C	68.00 ± 3.25	63.64 ± 2.94	64.43 ± 3.68	63.88 ± 3.44	65.83 ± 3.98	61.86 ± 3.68
Stroop CW	34.89 ± 2.55	31.55 ± 2.30	31.43 ± 2.89	31.75 ± 2.70	37.50 ± 3.12	33.86 ± 2.89
			Glucose solution			
CVLT-II Imm	28.89 ± 2.87	33.73 ± 2.60	33.29 ± 3.25	33.50 ± 3.04	38.17 ± 3.51	33.71 ± 3.25
CVLT-II Inte	4.78 ± 0.61	4.64 ± 0.56	5.86 ± 0.70	3.88± 0.65	6.00 ± 0.75	4.86 ± 0.70
CVLT-II Del	7.39 ± 0.94	7.61 ± 0.85	7.89 ± 1.06	8.34 ± 1.00	7.08 ± 1.15	7.29 ± 1.06
CVLT-II Hits	13.33 ± 0.74	12.55 ± 0.67	12.71 ± 0.84	12.00 ± 0.79	13.33 ± 0.91	13.86 ± 0.84
CVLT-II FP	7.78 ± 1.65	6.36 ± 1.49	6.29 ± 1.87	3.13 ± 1.75	5.67 ± 2.02	7.14 ± 1.87
CVLT-II Intru	9.89 ± 2.35	10.91 ± 2.13	6.57 ± 2.67	8.75 ± 2.50	6.83 ± 2.88	6.00 ± 2.67
SSpan Fwd	9.00 ± 0.52	8.18 ± 0.47	8.00 ± 0.59	7.00 ± 0.55	7.17 ± 0.64	7.71 ± 0.59
SSpan Bwd	7.22 ± 0.53	6.91 ± 0.48	6.29 ± 0.60	6.50 ± 0.56	6.67 ± 0.65	6.43 ± 0.60
Grooved Peg	155.44 ± 12.90	193.27 ± 11.66	180.43 ± 14.62	170.69 ± 13.68	155.25 ± 15.79	214.21 ± 14.62
MBPT 9	21.56 ± 1.74	22.46 ± 1.58	21.29 ± 1.97	17.38 ± 1.85	25.50 ± 2.13	18.00 ± 1.97
MBPT 36	20.22 ± 2.31	20.82 ± 2.09	21.00 ± 2.62	14.88 ± 2.45	21.67 ± 2.83	15.14 ± 2.62
LM Recall	9.50 ± 1.45	13.05 ± 1.31	12.21 ± 1.64	11.88 ± 1.54	15.33 ± 1.77	11.14 ± 1.64
Arithmetic	14.11 ± 1.09	16.36 ± 0.98	14.43 ± 1.23	12.38 ± 1.15	15.00 ± 1.33	13.86 ± 1.23
DSpan Fwd	11.33 ± 0.76	11.09 ± 0.69	9.29 ± 0.87	8.88 ± 0.81	9.00 ± 0.94	9.86 ± 0.87
DSpan Bwd	7.67 ± 0.75	7.55 ± 0.68	7.57 ± 0.85	5.63 ± 0.79	6.83 ± 0.92	5.71 ± 0.85
LNS	9.44 ± 0.76	10.82 ± 0.69	9.14 ± 0.87	9.63 ± 0.81	9.50 ± 0.94	8.29 ± 0.87
Stroop W	94.00 ± 5.16	96.00 ± 4.67	92.14 ± 5.85	85.88 ± 5.47	98.67 ± 6.32	92.29 ± 5.85
Stroop C	67.56 ± 3.96	65.00 ± 3.58	60.86 ± 4.49	58.88 ± 4.20	64.83 ± 4.84	60.29 ± 4.49
Stroop CW	37.00 ± 2.73	32.36 ± 2.47	32.57 ± 3.10	31.38 ± 2.90	35.00 ± 3.35	31.57 ± 3.10

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Table 11

Results of Multivariate Analysis examining Cognitive Performance as a Function of Glucose Dose, Glucoregulation, Age and Drinking Solution

Main effects and interactions	Wilks' Lambda multivariate test
Between subjects	
Age group	$F(19,73) = 2.09, p < .02$
Glucose dose	$F(38,146) = 1.02, p = .45$
Glucoregulation	$F(19,73) = 1.32, p = .20$
Age group * Glucose dose	$F(38,146) = 0.95, p = .56$
Age group * Glucoregulation	$F(19,73) = 0.87, p = .62$
Glucose dose * Glucoregulation	$F(38,146) = 1.16, p = .27$
Age group * Glucose dose * Glucoregulation	$F(38,146) = 0.80, p = .78$
Within subjects	
Solution	$F(19,73) = 0.88, p = .60$
Solution * Age group	$F(19,73) = 1.23, p = .26$
Solution * Glucose dose	$F(38,146) = 1.44, p = .07$
Solution * Glucoregulation	$F(19,73) = 1.05, p = .42$
Solution * Age group * Glucose dose	$F(38,146) = 0.89, p = .66$
Solution * Age group * Glucoregulation	$F(19,73) = 1.29, p = .21$
Solution * Glucose dose * Glucoregulation	$F(38,146) = 1.38, p = .09$
Solution * Age group * Glucose dose * Glucoregulation	$F(38,146) = 0.84, p = .73$

Measures of attention and working memory. There was a significant main effect of age on Spatial Span backward (*F*(1, 91) = 5.24, $p < .03$; $d = 0.46$), Arithmetic (*F*(1, 91) = 4.54, $p < .04$; $d = 0.42$) and the Stroop Colour-Word (*F*(1, 91) = 10.94, $p < .01$; $d = 0.65$), with younger participants obtaining higher scores (Spatial Span Backward: $M = 7.56$, $SE = 0.20$; Arithmetic: $M = 15.63$, $SE = 0.43$; Stroop Colour-Word: $M = 38.33$, $SE = 1.03$) than older participants (Spatial Span Backward: $M = 6.89$, $SE = 0.21$; Arithmetic: $M = 14.29$, $SE = 0.45$; Stroop Colour-Word: $M = 33.40$, $SE = 1.08$). There was also a significant main effect of glucose dose for Digit Span Forward (*F*(2, 91) = 4.05, $p < .03$). Pairwise comparisons (Bonferroni adjustment) revealed that there was a significant difference between participants in the 300 mg/kg group ($M = 10.70$, $SE = 0.36$) and those in the 650 mg/kg group ($M = 9.29$, $SE = 0.35$; $d = 0.68$).

Two significant interactions were observed on the Spatial Span Forward, one between solution and glucose dose (*F*(2, 91) = 5.44, $p < .01$) and the other between glucoregulation and age group (*F*(1, 91) = 5.99, $p < .02$). Bonferroni planned comparisons revealed that for the interaction between solution and glucose (see Figure 3), participants in the 300 mg/kg group obtained higher scores following glucose ingestion ($M = 8.79$, $SE = 0.28$) compared to saccharin ingestion ($M = 8.18$, $SE = 0.27$; $d = 0.38$) whereas those in the 650 mg/kg group had a better performance after drinking the saccharin solution ($M = 8.09$, $SE = 0.26$) compared to the glucose solution ($M = 7.57$, $SE = 0.27$; $d = -0.33$). As for the interaction between glucoregulation and age (see Figure 4), planned comparisons indicated that younger worse regulators obtained higher scores on the Spatial Span Forward ($M = 8.80$, $SE = 0.29$) compared to older worse regulators ($M = 7.61$, $SE = 0.27$; $d = 0.86$).

A two-way interaction between solution and age group was observed on the Spatial Span Backward (*F*(1, 91) = 5.13, $p < .03$) and further explained by a three-way interaction between solution, glucoregulation and age group (*F*(1, 91) = 6.02, $p < .02$). Results from Bonferroni planned comparisons revealed several significant differences (see Figure 5). There was a significant difference between younger better regulators (saccharin: *M* = 7.48, *SE* = 0.30; glucose: *M* = 7.35, *SE* = 0.28) and older better regulators (saccharin: *M* = 6.79, *SE* = 0.36; glucose: *M* = 6.73, *SE* = 0.35) in the saccharin condition (*d* = 0.41) as well as in the glucose condition (*d* = 0.39), and between younger worse regulators (*M* = 8.04, *SE* = 0.35) and older worse regulators (*M* = 6.61, *SE* = 0.32) in the glucose condition (*d* = 0.87), with younger participants outperforming the older participants. Older better regulators obtained lower scores (*M* = 6.79, *SE* = 0.36) than older worse regulators (*M* = 7.42, *SE* = 0.34) in the saccharin condition (*d* = -0.37). Younger better regulators (*M* = 7.35, *SE* = 0.28) performed more poorly than younger worse regulators (*M* = 8.04, *SE* = 0.35) in the glucose condition (*d* = -0.42). Younger worse regulators obtained higher scores following glucose ingestion (*M* = 8.04, *SE* = 0.35) compared to saccharin ingestion (*M* = 7.36, *SE* = 0.36; *d* = 0.40). The reverse was true for older worse regulators, with performance being better in the saccharin condition (*M* = 7.42, *SE* = 0.34) than in the glucose condition (*M* = 6.61, *SE* = 0.32; *d* = -0.49).

There was also a significant three-way interaction between solution, glucoregulation and age group on the Digit Span Forward (*F*(1, 91) = 4.32, $p < .05$). Figure 6 shows that older worse regulators (*M* = 10.49, *SE* = 0.42) outperformed the older better regulators (*M* = 9.44, *SE* = 0.46) in the saccharin condition (*d* = -0.49).

Figure 3. Performance on the Spatial Span Forward as a function of solution and glucose dose.

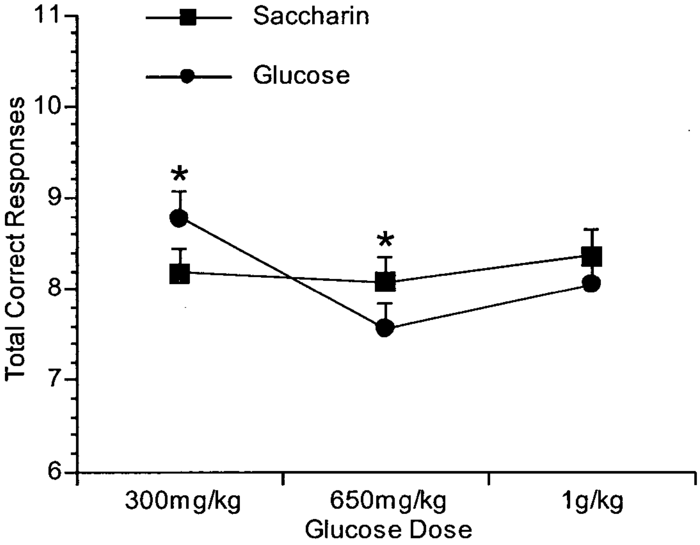


Figure 4. Performance on the Spatial Span Forward as a function of glucoregulation and age group.

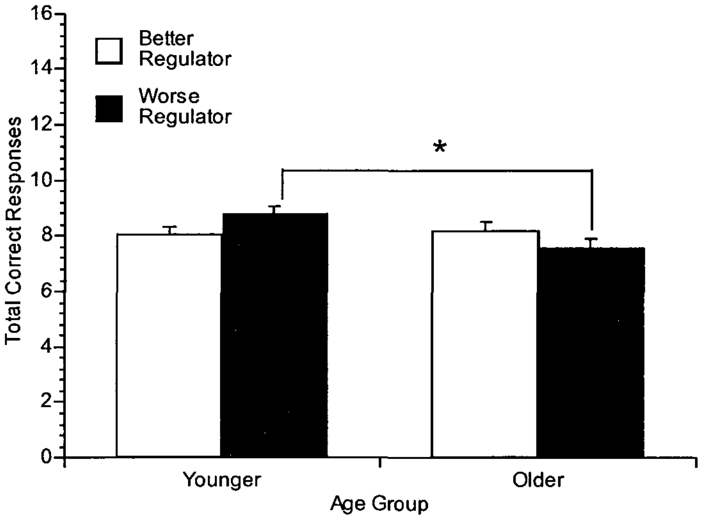


Figure 5. Performance on the Spatial Span Backward as a function of solution, glucoregulation and age group.

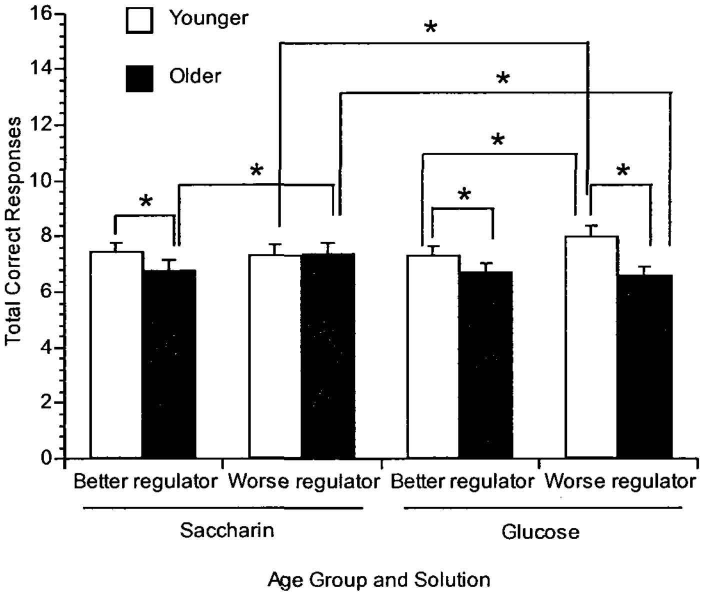
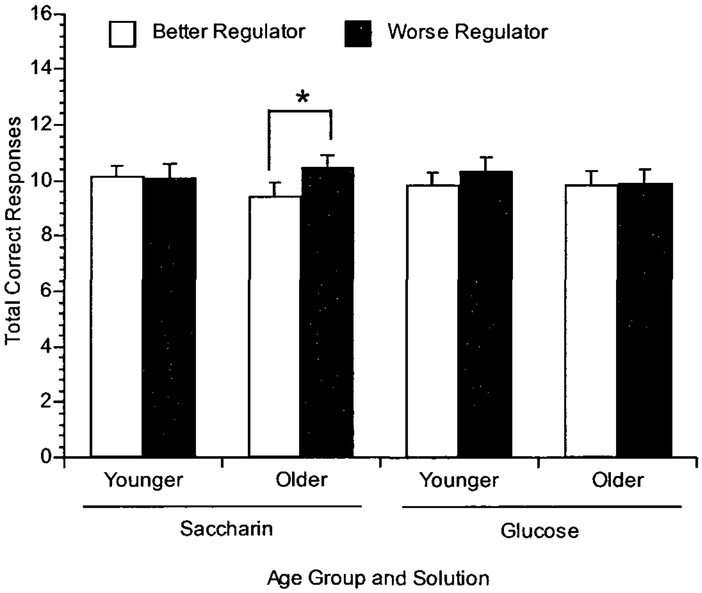


Figure 6. Performance on the Digit Span Forward as a function of solution, glucoregulation and age group.



Measures of learning and verbal memory. There was a significant main effect of age on the CVLT-II delayed recall ($F(1, 91) = 4.35, p < .05$; $d = 0.41$), with younger participants recalling more words ($M = 8.70$, $SE = 0.37$) compared to older participants ($M = 7.60$, $SE = 0.38$).

A two-way interaction between solution and glucose dose was observed on the CVLT-II immediate free recall ($F(2, 91) = 3.39, p < .04$). Bonferroni planned comparisons revealed that participants in the 1 g/kg group recalled more words in the glucose condition ($M = 36.63$, $SE = 1.53$) than in the saccharin condition ($M = 33.31$, $SE = 1.59$; $d = 0.37$) as illustrated in Figure 7.

A three-way interaction between solution, glucose dose and glucoregulation was obtained on the CVLT-II recognition hits ($F(2, 91) = 3.34, p < .05$). Figure 8 demonstrates that worse regulators in the 1 g/kg group had a better recognition hits score in the glucose condition ($M = 13.71$, $SE = 0.56$) than in the saccharin condition ($M = 12.45$, $SE = 0.50$; $d = 0.59$).

The only significant effect for the Logical Memory task was an interaction between glucose dose and glucoregulation ($F(2, 91) = 3.19, p < .05$). However, Bonferroni planned comparisons did not reveal any significant differences. Figure 9 shows there was a trend for better performance of better regulators compared to the worse regulators in the participants who received the 1 g/kg dose.

Figure 7. Performance on the CVLT-II Total Immediate Free Recall as a function of solution and glucose dose.

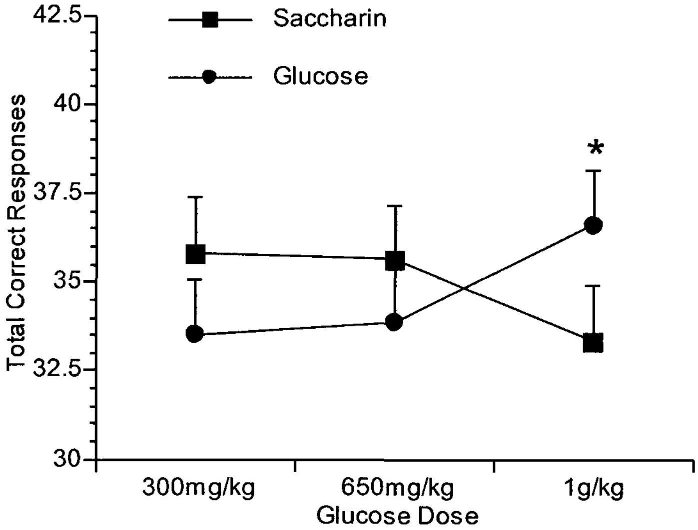


Figure 8. Performance on the CVLT-II Long-Delay Recognition Hits as a function of solution, glucose dose and glucoregulation.

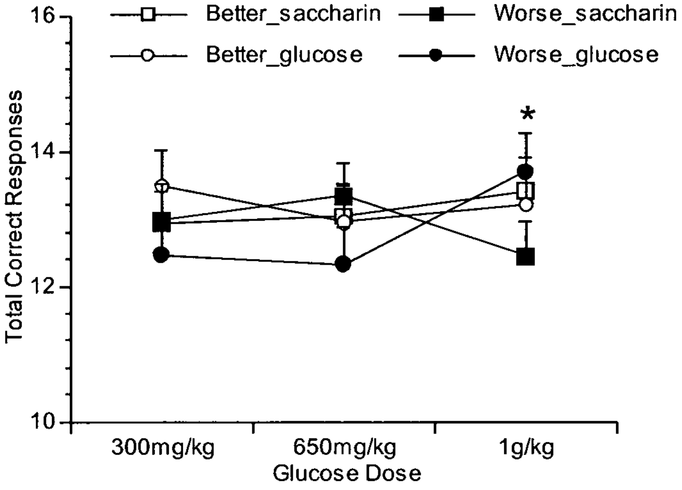
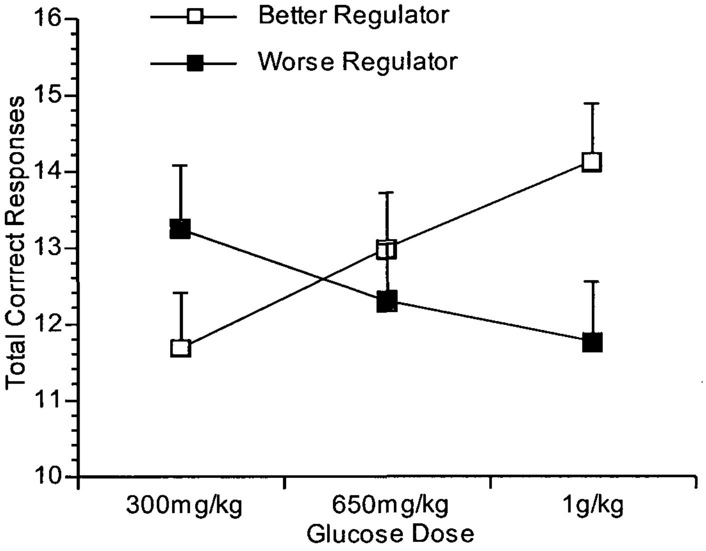
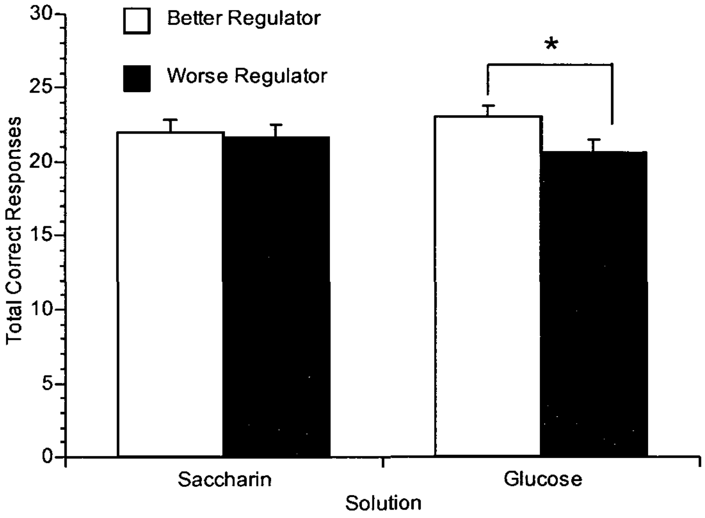


Figure 9. Performance on the Logical Memory Immediate and Delayed Recall as a function of glucose dose and glucoregulation.



Measure of executive functioning. There was a significant main effect of age on MBPT 36 seconds ($F(1, 91) = 4.46, p < .04; d = 0.42$), with younger participants remembering more consonants ($M = 21.97, SE = 0.89$) than older participants ($M = 19.23, SE = 0.94$). Furthermore, a two-way interaction between solution and glucoregulation was obtained on the MBPT 9 seconds ($F(1, 91) = 4.51, p < .04$). Bonferroni planned comparisons indicated that better regulators ($M = 23.08, SE = 0.73$) recalled more consonants than worse regulators ($M = 20.65, SE = 0.77; d = 0.45$) following glucose ingestion (see Figure 10).

Figure 10. Performance on the Modified Brown-Peterson Task 9 seconds as a function of solution and glucoregulation.



Measure of fine motor skills. There was a significant main effect of age on the Grooved Pegboard ($F(1, 91) = 26.11, p < .01; d = 1.01$), with younger participants completing the task more quickly ($M = 137.84$, $SE = 4.84$) compared to older participants ($M = 173.69$, $SE = 5.08$). There was also a significant main effect of solution on the Grooved Pegboard ($F(1, 91) = 4.55, p < .04$), with participants completing the task faster in the saccharin condition ($M = 153.20$, $SE = 3.47$) compared to the glucose condition ($M = 158.33$, $SE = 3.93$).

Several significant interactions were observed on this measure. There was a two-way interaction between solution and glucose dose ($F(2, 91) = 5.08, p < .01$) which was further explained by a three-way interaction between solution, glucose dose and age group ($F(2, 91) = 4.17, p < .02$). Bonferroni planned comparisons indicated that older participants in the 1 g/kg group took significantly more time to complete the task following glucose ingestion ($M = 184.73$, $SE = 10.76$) compared to when they received the saccharin solution ($M = 155.66$, $SE = 9.50$; $d = -0.79$) as illustrated in Figure 11.

A three-way interaction between solution, glucose dose and glucoregulation was also observed ($F(2, 91) = 6.03, p < .01$). Planned comparisons revealed that worse regulators in the 1 g/kg group were slower in the glucose condition ($M = 178.77$, $SE = 9.75$) compared to the saccharin condition ($M = 150.13$, $SE = 8.61$; $d = -0.78$). Furthermore, there was a significant difference between better and worse regulators in the 1 g/kg group in the glucose condition, with better regulators ($M = 142.25$, $SE = 9.67$) completing the task more quickly compared to worse regulators ($M = 178.77$, $SE = 9.75$; $d = 0.91$). Results are presented in Figure 12.

Finally, there was a two-way interaction between glucoregulation and age group ($F(1, 91) = 4.31, p < .05$). Figure 13 shows that the older worse regulators ($M = 185.35$, $SE = 6.89$)

took more time to complete this task compared to younger worse regulators (*M* = 134.93, *SE* = 7.48; *d* = 1.42).

Figure 11. Performance on the Grooved Pegboard Total as a function of solution, glucose dose and age group.

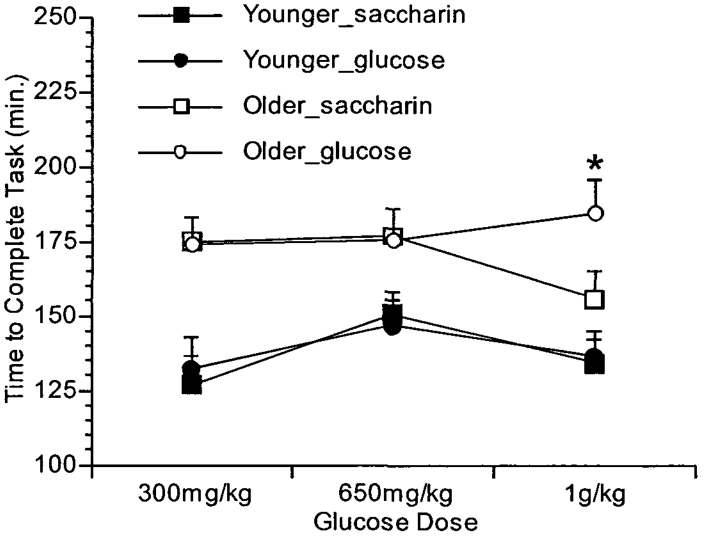


Figure 12. Performance on the Grooved Pegboard Total as a function of solution, glucose dose and glucoregulation.

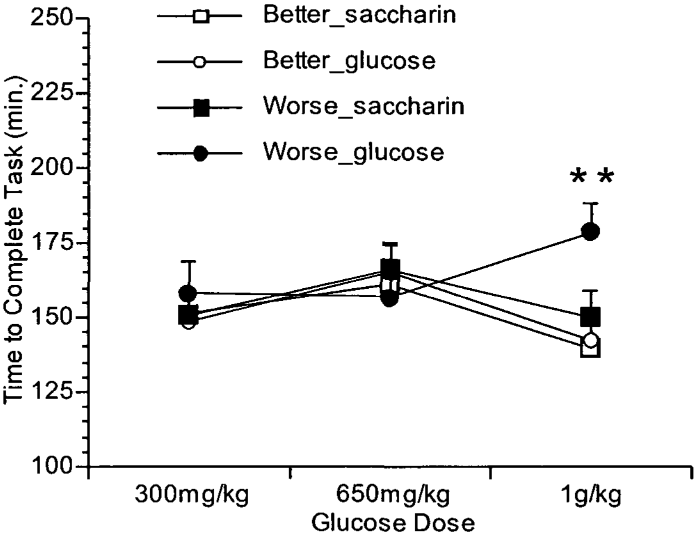
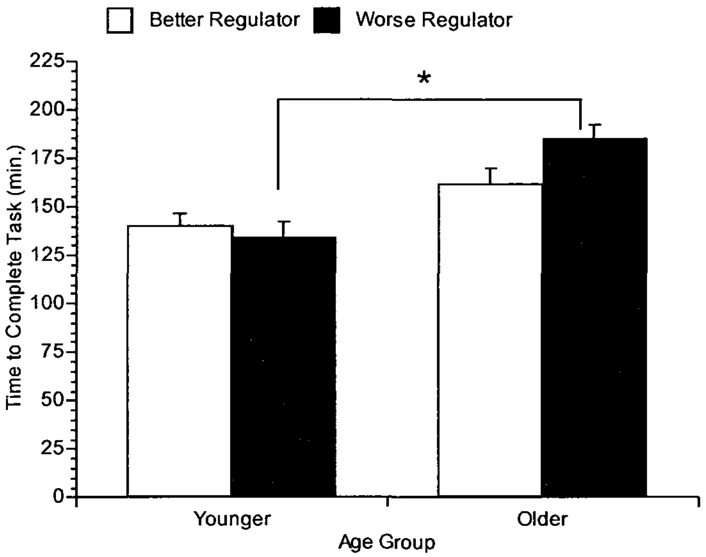


Figure 13. Performance on the Grooved Pegboard Total as a function of glucoregulation and age group.



First testing session

Data from the first testing session was also analyzed to examine whether results from this analysis would replicate findings from previous research using a between-subjects design. Multivariate analysis of variance (MANOVA) was conducted with the between-subject factors of solution (saccharin vs. glucose, irrespective of glucose dose received), glucoregulation (better vs. worse) and age (younger vs. older). Wilks' Lambda multivariate tests were all non-significant (solution: $F(19, 77) = 1.72, p = .05$; glucoregulation: $F(19, 77) = 0.86, p = .63$; age: $F(19, 77) = 0.60, p = .90$; solution and glucoregulation: $F(19, 77) = 1.41, p = .15$; solution and age: $F(19, 77) = .26, p = .99$; glucoregulation and age: $F(19, 77) = 1.28, p = .22$; solution and glucoregulation and age: $F(19, 77) = 1.12, p = .35$).

Cognitive performance in the saccharin condition

Performance during the saccharin condition was analyzed separately to examine the hypothesis that glucoregulation modulates cognitive performance. Multivariate analysis of variance (MANOVA) was conducted with the between-subject factors of glucoregulation (better vs. worse) and age (younger vs. older). Wilks' Lambda multivariate test was significant only for age (age: $F(19, 81) = 2.38, p < .01$; glucoregulation: $F(19, 81) = 0.77, p = .74$; age and glucoregulation: $F(19, 81) = 0.84, p = .65$).

Direction of means

The direction of the means was also examined for each a priori hypothesis to gain a better understanding of the trends given the limited statistically significant findings. The main effects of solution, glucoregulation and age are presented in Table 12. As expected, the younger group outperformed the older group on all the cognitive measures. Participants categorized as better glucoregulators also obtained superior performance on 14 out of the 19 neuropsychological variables compared to worse glucoregulators. However, inspection of the means revealed that performance was rarely higher following glucose ingestion compared to saccharin. Since participants were given one of three doses of glucose, it is possible that the overall means masked increased performance in the glucose condition. Therefore, the means for the interaction between glucose dose and solution are presented in Table 13. Increased performance following glucose ingestion compared to saccharin ingestion was more frequent in the 300 mg/kg and 1 g/kg groups than in the 650 mg/kg group. Age and glucoregulation could have also mediated the impact of glucose on cognitive performance. When examining the interaction between age and solution (see Table 14), there is no clear pattern, with means following glucose ingestion being higher than following saccharin ingestion at similar frequencies in both age groups. As for the interaction between glucoregulation and solution (see Table 15), better regulators seemed to benefit more from glucose ingestion than worse regulators. The direction of the means for the interaction between glucoregulation and age (see Table 15) suggests that better regulators outperformed worse regulators on more measures in the older group compared to the younger group. Finally, the three-way interaction between age, glucoregulation and solution (see Table 16) shows that the frequency of measures benefiting from glucose ingestion is comparable between younger better regulators and older better regulators. However, there is a difference between worse regulators of both age groups, with a higher number of measures being facilitated by glucose in the older worse regulators.

The direction of the means for the interaction between glucoregulation and age was examined further by looking at scores obtained on the cognitive measures in the saccharin condition only (see Table 17). The pattern is very similar to the one observed in Table 15 (average of performance in the saccharin and the glucose conditions); better regulators outperformed worse regulators on more measures in the older group (total of 14) compared to the younger group (total of 11).

Table 12

Direction of Means (Better Performance > Worse Performance; difference between the means in parenthesis) for the Main Effects of Solution, Glucoregulation and Age for each Cognitive Measure

	Solution	Glucoregulation	Age
CVLT-II Imm	saccharin>glucose (0.238)	**better>worse (1.563)**	**younger>older (2.571)**
CVLT-II Inte	**glucose>saccharin (0.288)**	**better>worse (0.597)**	**younger>older (0.525)**
CVLT-II Del	saccharin>glucose (0.155)	**better>worse (0.236)**	**younger>older (1.104)**
CVLT-II Hits	saccharin>glucose (0.002)	**better>worse (0.296)**	**younger>older (0.529)**
CVLT-II FP	**glucose>saccharin (0.527)**	**better>worse (0.510)**	**younger>older (0.859)**
CVLT-II Intru	saccharin>glucose (0.161)	worse>better (0.654)	**younger>older (1.683)**
SSpan Fwd	saccharin>glucose (0.077)	worse>better (0.057)	**younger>older (0.519)**
SSpan Bwd	saccharin>glucose (0.083)	worse>better (0.269)	**younger>older (0.671)**
Grooved Peg	saccharin>glucose (5.126)	**better>worse (8.751)**	**younger>older (35.852)**
MBPT 9	saccharin>glucose (0.008)	**better>worse (1.370)**	**younger>older (1.676)**
MBPT 36	saccharin>glucose (0.395)	**better>worse (1.157)**	**younger>older (2.734)**
LM Recall	saccharin>glucose (0.912)	**better>worse (0.493)**	**younger>older (0.558)**
Arithmetic	saccharin>glucose (0.137)	**better>worse (0.766)**	**younger>older (1.335)**
DSpan Fwd	saccharin>glucose (0.049)	worse>better (0.386)	**younger>older (0.185)**
DSpan Bwd	saccharin>glucose (0.058)	**better>worse (0.421)**	**younger>older (0.688)**
LNS	**glucose>saccharin (0.303)**	worse>better (0.038)	**younger>older (0.673)**
Stroop W	**glucose>saccharin (0.348)**	**better>worse (2.620)**	**younger>older (3.314)**
Stroop C	saccharin>glucose (0.966)	**better>worse (1.487)**	**younger>older (2.958)**
Stroop CW	**glucose>saccharin (0.076)**	**better>worse (2.096)**	**younger>older (4.923)**

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Table 13

Direction of Means (Better Performance> Worse Performance; difference between the means in parenthesis) for the Interaction between Glucose Dose and Solution for each Cognitive Measure

	Glucose dose*Solution		
	300 mg/kg	650 mg/kg	1 g/kg
CVLT-II Imm	saccharin>glucose (2.276)	saccharin>glucose (1.761)	**glucose>saccharin (3.323)**
CVLT-II Inte	**glucose>saccharin (0.378)**	saccharin>glucose (0.152)	**glucose>saccharin (0.637)**
CVLT-II Del	saccharin>glucose (0.138)	saccharin>glucose (0.376)	**glucose>saccharin (0.048)**
CVLT-II Hits	**glucose>saccharin (0.023)**	saccharin>glucose (0.552)	**glucose>saccharin (0.522)**
CVLT-II FP	**glucose>saccharin (0.437)**	**glucose>saccharin (0.904)**	**glucose>saccharin (0.239)**
CVLT-II Intru	**glucose>saccharin (0.251)**	**glucose>saccharin (0.403)**	saccharin>glucose (1.137)
SSpan Fwd	**glucose>saccharin (0.607)**	saccharin>glucose (0.518)	saccharin>glucose (0.319)
SSpan Bwd	**glucose>saccharin (0.107)**	saccharin>glucose (0.029)	saccharin>glucose (0.326)
Grooved Peg	saccharin>glucose (2.311)	**glucose>saccharin (2.497)**	saccharin>glucose (15.563)
MBPT 9	saccharin>glucose (0.001)	saccharin>glucose (0.564)	**glucose>saccharin (0.542)**
MBPT 36	**glucose>saccharin (0.832)**	saccharin>glucose (1.448)	saccharin>glucose (0.568)
LM Recall	saccharin>glucose (0.740)	saccharin>glucose (1.400)	saccharin>glucose (0.598)
Arithmetic	saccharin>glucose (0.488)	saccharin>glucose (0.497)	**glucose>saccharin (0.571)**
DSpan Fwd	**glucose>saccharin (0.085)**	**glucose>saccharin (0.018)**	saccharin>glucose (0.250)
DSpan Bwd	saccharin>glucose (0.061)	**glucose>saccharin (0.145)**	saccharin>glucose (0.260)
LNS	**glucose>saccharin (0.201)**	**glucose>saccharin (0.648)**	**glucose>saccharin (0.059)**
Stroop W	**glucose>saccharin (0.766)**	saccharin>glucose (1.477)	**glucose>saccharin (1.753)**
Stroop C	saccharin>glucose (0.454)	saccharin>glucose (2.615)	**glucose>saccharin (0.170)**
Stroop CW	**glucose>saccharin (1.682)**	saccharin>glucose (0.472)	saccharin>glucose (0.982)

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Table 14

Direction of Means (Better Performance> Worse Performance; difference between the means in parenthesis) for the Interaction between Age and Solution for each Cognitive Measure

	Age*Solution	
	Younger	Older
CVLT-II Imm	saccharin>glucose (0.551)	**glucose>saccharin (0.075)**
CVLT-II Inte	**glucose>saccharin (0.111)**	**glucose>saccharin (0.465)**
CVLT-II Del	saccharin>glucose (0.316)	**glucose>saccharin (0.005)**
CVLT-II Hits	saccharin>glucose (0.403)	**glucose>saccharin (0.398)**
CVLT-II FP	**glucose>saccharin (0.023)**	**glucose>saccharin (1.031)**
CVLT-II Intru	**glucose>saccharin (1.096)**	saccharin>glucose (1.419)
SSpan Fwd	saccharin>glucose (0.008)	saccharin>glucose (0.144)
SSpan Bwd	**glucose>saccharin (0.273)**	saccharin>glucose (0.438)
Grooved Peg	saccharin>glucose (1.196)	saccharin>glucose (9.054)
MBPT 9	saccharin>glucose (0.011)	saccharin>glucose (0.005)
MBPT 36	saccharin>glucose (0.229)	saccharin>glucose (0.560)
LM Recall	saccharin>glucose (1.398)	saccharin>glucose (0.427)
Arithmetic	saccharin>glucose (0.400)	**glucose>saccharin (0.125)**
DSpan Fwd	saccharin>glucose (0.043)	saccharin>glucose (0.054)
DSpan Bwd	**glucose>saccharin (0.149)**	saccharin>glucose (0.266)
LNS	**glucose>saccharin (0.251)**	**glucose>saccharin (0.354)**
Stroop W	**glucose>saccharin (0.774)**	saccharin>glucose (0.079)
Stroop C	saccharin>glucose (0.228)	saccharin>glucose (1.704)
Stroop CW	**glucose>saccharin (0.334)**	saccharin>glucose (0.181)

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Table 15

Direction of Means (Better Performance> Worse Performance; difference between the means in parenthesis) for the Interaction between Glucoregulation and Solution as well as the Interaction between Glucoregulation and Age for each Cognitive Measure

	Glucoregulation*Solution		Glucoregulation*Age	
	Better	Worse	Younger	Older
CVLT-II Imm	sac>glu (0.665)	**glu>sac (0.189)**	**better>worse (1.422)**	**better>worse (1.703)**
CVLT-II Inte	**glu>sac (0.510)**	**glu>sac (0.066)**	**better>worse (0.467)**	**better>worse (0.726)**
CVLT-II Del	sac>glu (0.192)	sac>glu (0.119)	**better>worse (0.452)**	**better>worse (0.021)**
CVLT-II Hits	**glu>sac (0.083)**	sac>glu (0.088)	**better>worse (0.217)**	**better>worse (0.375)**
CVLT-II FP	**glu>sac (0.262)**	**glu>sac (0.791)**	**better>worse (1.353)**	worse>better (0.333)
CVLT-II Intru	**glu>sac (1.016)**	sac>glu (1.339)	worse>better (0.378)	worse>better (0.929)
SSpan Fwd	sac>glu (0.333)	**glu>sac (0.180)**	worse>better (0.730)	**better>worse (0.618)**
SSpan Bwd	sac>glu (0.098)	sac>glu (0.067)	worse>better (0.282)	worse>better (0.258)
Grooved Peg	sac>glu (1.481)	sac>glu (8.771)	worse>better (5.811)	**better>worse (23.314)**
MBPT 9	**glu>sac (1.046)**	sac>glu (1.061)	**better>worse (0.043)**	**better>worse (2.698)**
MBPT 36	**glu>sac (0.206)**	sac>glu (0.995)	worse>better (0.887)	**better>worse (3.201)**
LM Recall	sac>glu (0.812)	sac>glu (1.012)	**better>worse (0.274)**	**better>worse (0.713)**
Arithmetic	sac>glu (0.176)	sac>glu (0.099)	**better>worse (0.947)**	**better>worse (0.585)**
DSpan Fwd	**glu>sac (0.067)**	sac>glu (0.165)	worse>better (0.213)	worse>better (0.559)
DSpan Bwd	**glu>sac (0.173)**	sac>glu (0.291)	**better>worse (0.168)**	**better>worse (0.674)**
LNS	**glu>sac (0.383)**	**glu>sac (0.222)**	worse>better (0.033)	worse>better (0.043)
Stroop W	**glu>sac (1.990)**	sac>glu (1.295)	**better>worse (3.290)**	**better>worse (1.950)**
Stroop C	sac>glu (1.017)	sac>glu (0.917)	worse>better (0.022)	**better>worse (2.996)**
Stroop CW	**glu>sac (0.827)**	sac>glu (0.674)	**better>worse (1.537)**	**better>worse (2.654)**

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word; sac = saccharin; glu = glucose.

Table 16

Direction of Means (Better Performance> Worse Performance; difference between the means in parenthesis) for the Interaction between Age, Glucoregulation and Solution for each Cognitive Measure

	Age*Glucoregulation*Solution			
	Younger		Older	
	Better	Worse	Better	Worse
CVLT-II Imm	**glu>sac (0.498)**	sac>glu (1.600)	sac>glu (1.828)	**glu>sac (1.978)**
CVLT-II Inte	**glu>sac (0.192)**	**glu>sac (0.030)**	**glu>sac (0.828)**	**glu>sac (0.102)**
CVLT-II Del	sac>glu (0.075)	sac>glu (0.558)	sac>glu (0.308)	**glu>sac (0.319)**
CVLT-II Hits	sac>glu (0.182)	sac>glu (0.622)	**glu>sac (0.349)**	**glu>sac (0.448)**
CVLT-II FP	**glu>sac (0.194)**	sac>glu (0.148)	**glu>sac (0.330)**	**glu>sac (1.730)**
CVLT-II Intru	**glu>sac (1.734)**	**glu>sac (0.459)**	**glu>sac (0.298)**	sac>glu (3.136)
SSpan Fwd	sac>glu (0.328)	**glu>sac (0.312)**	sac>glu (0.338)	**glu>sac (0.049)**
SSpan Bwd	sac>glu (0.128)	**glu>sac (0.674)**	sac>glu (0.069)	sac>glu (0.808)
Grooved Peg	**glu>sac (0.388)**	sac>glu (2.781)	sac>glu (3.351)	sac>glu (14.759)
MBPT 9	**glu>sac (1.290)**	sac>glu (1.311)	**glu>sac (0.801)**	sac>glu (0.810)
MBPT 36	**glu>sac (0.156)**	sac>glu (0.615)	**glu>sac (0.257)**	sac>glu (1.377)
LM Recall	sac>glu (0.815)	sac>glu (1.981)	sac>glu (0.811)	sac>glu (0.043)
Arithmetic	sac>glu (0.207)	sac>glu (0.593)	sac>glu (0.146)	**glu>sac (0.395)**
DSpan Fwd	sac>glu (0.301)	**glu>sac (0.214)**	**glu>sac (0.436)**	sac>glu (0.545)
DSpan Bwd	**glu>sac (0.224)**	**glu>sac (0.074)**	**glu>sac (0.122)**	sac>glu (0.654)
LNS	**glu>sac (0.583)**	sac>glu (0.081)	**glu>sac (0.182)**	**glu>sac (0.525)**
Stroop W	**glu>sac (2.459)**	sac>glu (0.911)	**glu>sac (1.522)**	sac>glu (1.679)
Stroop C	sac>glu (0.361)	sac>glu (0.096)	sac>glu (1.672)	sac>glu (1.736)
Stroop CW	**glu>sac (1.401)**	sac>glu (0.733)	**glu>sac (0.251)**	sac>glu (0.614)

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word; sac = saccharin; glu = glucose.

Table 17

Direction of Means (Better Performance> Worse Performance; difference between the means in parenthesis) for the Interaction between Glucoregulation and Age for each Cognitive Measure in the Saccharin Condition

	Glucoregulation*Age	
	Younger	Older
CVLT-II Imm	**better>worse (0.418)**	**better>worse (2.930)**
CVLT-II Inte	**better>worse (0.319)**	**better>worse (0.297)**
CVLT-II Del	**better>worse (0.365)**	**better>worse (0.170)**
CVLT-II Hits	worse>better (0.009)	**better>worse (0.297)**
CVLT-II FP	**better>worse (1.465)**	**better>worse (0.172)**
CVLT-II Intru	worse>better (0.949)	worse>better (2.658)
SSpan Fwd	worse>better (0.371)	**better>worse (0.794)**
SSpan Bwd	**better>worse (0.109)**	worse>better (0.644)
Grooved Peg	worse>better (3.604)	**better>worse (18.537)**
MBPT 9	worse>better (1.261)	**better>worse (1.556)**
MBPT 36	worse>better (1.159)	**better>worse (1.465)**
LM Recall	**better>worse (0.063)**	**better>worse (0.913)**
Arithmetic	**better>worse (0.765)**	**better>worse (0.567)**
DSpan Fwd	worse>better (0.049)	worse>better (1.154)
DSpan Bwd	**better>worse (0.085)**	**better>worse (0.119)**
LNS	worse>better (0.301)	worse>better (0.133)
Stroop W	**better>worse (1.911)**	worse>better (0.087)
Stroop C	**better>worse (1.147)**	**better>worse (3.042)**
Stroop CW	**better>worse (0.587)**	**better>worse (2.269)**

Note. CVLT-II Imm = CVLT-II Total Immediate Free Recall; CVLT-II Inte = CVLT-II Free Recall of Interference List; CVLT-II Del = CVLT-II Short and Long-Delay Free and Cued Recall; CVLT-II Hits = CVLT-II Long-Delay Recognition Hits; CVLT-II FP = CVLT-II Long-Delay Recognition False-Positives; CVLT-II Intru = CVLT-II Total Intrusions; SSpan Fwd = Spatial Span Forward; SSpan Bwd = Spatial Span Backward; Grooved Peg = Grooved Pegboard Total; MBPT 9 = Modified Brown-Peterson Task 9 seconds; MBPT 36 = Modified Brown-Peterson Task 36 seconds; LM Recall = Logical Memory Immediate and Delayed Recall; DSpan Fwd = Digit Span Forward; DSpan Bwd = Digit Span Backward; LNS = Letter-Number Sequencing; Stroop W = Stroop Word; Stroop C = Stroop Colour; Stroop CW = Stroop Colour-Word.

Discussion

The purpose of this study was to further examine the conditions in which glucose facilitation is observed. We used three doses of glucose adjusted to body weight, included tasks requiring dual processing, measured glucose regulation and examined whether age would interact with glucoregulation to mediate the glucose enhancing effect on cognitive performance. Statistical analyses revealed a small number of significant differences. The multivariate analysis indicated only an overall significant effect of age group. Significant results from the univariate analyses were therefore examined to gain a better understanding of the data and offer possible insights for future research.

Solution and dosage

The first objective of this study was to explore further the impact of glucose on cognitive performance by using three doses of glucose (300 mg/kg, 650 mg/kg and 1 g/kg) adjusted to body weight. Previously, only three studies compared several doses of glucose (Flint & Turek, 2003; Messier et al., 1998; Parsons & Gold, 1992). Of those, one study in older adults used three absolute doses of glucose (unadjusted for weight) showing that 25 g enhanced story recall whereas 10 g and 50 g failed to improve memory performance compared to the saccharin condition (Parsons & Gold, 1992). Based on a recent review indicating that younger adults usually benefit more from lower doses of glucose whereas glucose facilitation is typically observed with higher doses in older adults (Messier, 2004), it was hypothesized that higher doses of glucose would be more effective in this sample of older adults. However, results obtained showed no statistically significant effect of solution on cognitive performance, irrespective of glucose dose administered. There was a trend for increased performance following 300 mg/kg of glucose on Spatial Span Forward and in the 1 g/kg glucose group on the CVLT-II immediate free recall. Some previous studies have failed to observe enhanced cognitive performance following glucose ingestion (Azari, 1991; Benton & Owens, 1993; Flint & Turek, 2003; Ford et al., 2002; Owens & Benton, 1994). Interestingly, glucose did not facilitate recall of contextual information (paragraph recall) as had been demonstrated in many studies examining the impact of glucose on the cognitive performance of healthy younger adults (Craft et al., 1994) and older adults (Craft et al., 1994; Craft et al., 1992; Gonder-Frederick et al., 1987; Manning et al., 1992; Manning, Stone et al., 1998; Parsons & Gold, 1992). It could be hypothesized that different doses of glucose affect different cognitive domains. However, the review of studies summarized in Appendix A does not support this assumption since improvements on memory measures have been observed with 25 g, 50 g and 75 g of glucose and no pattern was noticeable with other cognitive domains albeit research is more limited with tasks assessing cognitive abilities other than episodic verbal memory.

Additionally, a trend for decreased performance following 650 mg/kg of glucose was observed on the Spatial Span Forward. Overall, glucose appeared to impair performance on the Grooved Pegboard, particularly worse regulators and older participants. Studies conducted in animals have demonstrated that glucose can have impairing effects on memory performance (Erickson, Watts, & Parent, 2006; Rodriguez et al., 1994). This was also observed in younger adults, more specifically men with good glucoregulation (Craft et al., 1994).

Although previous studies investigating the impact of ingested glucose on cognition have generally observed a glucose facilitation effect on cognitive functioning with memory being the most studied and showing the most robust findings, the caveat is that research in this area has mostly used fixed doses of glucose. It is possible that the glucose doses used in the present study were too far from the 50 g dose that has been used most successfully in older people. The 650 mg/kg dose would be comparable to the fixed 50 g dose only in people weighing 76.92 kg; in an 90 kg individual, the dose would actually be 58.50 g. Previous animal work has indicated sharp dose-response curves (Messier & White, 1987; Rodriguez et al., 1994) since a 2 g/kg dose improved memory but not a higher (3 g/kg) or lower (1 g/kg) dose. This suggests that the effect of glucose on human cognition could also be limited to a narrow range of doses. The present experiment explored a good range of doses but in the lower portion of the dose-response curve. Therefore, it is possible that a slightly different dosage could have been facilitative.

Finally, the presence of significant practice effects on more than half of the cognitive variables could have reduced the ability of these tests to measure an improvement because of the associated increased variability in test-retest situations where the test order is randomized. This problem was explored for two tests of visual memory (Rey or Taylor complex figures) and it was found that the size of the practice effects depended on which test was presented first (Awad, Tsiakas et al., 2004). Since practice effects were not present on all tasks or were of the same magnitude, it is unlikely that practice effects were the sole explanation of the absence of significant effects of glucose on cognition. Even though the present sample size is too small to investigate this question (and the design is not appropriate), it would be interesting to examine whether glucose increases the practice effects observed when tests are repeated in a short interval.

Dual tasks

Another aim of this study was to include cognitive measures involving a concomitant or interference task in the battery of tests to examine whether the glucose facilitation effect would be more readily observable on tasks that require dual processing. Studies conducted in younger adults have observed a glucose facilitation effect on recall of a list of words only when the participants were asked to perform a concomitant task during the learning phase of the verbal memory task (Foster et al., 1998; Sunram-Lea et al., 2002b). Findings from previous studies could be explained by the high demand placed on a limited number of cognitive resources which would result in decreased performance on cognitive testing. However, when cognitive tasks require a high level of cognitive resources and energy but the brain cannot meet those demands, it is thought that the ingestion of glucose could allow the brain to perform optimally since there would be an increase in energy, thus allowing the brain to function better. Hence, it was hypothesized that the glucose facilitation effect would be more pronounced on tasks that required dual processing. Three tests presented this type of situation: the CVLT-II performed while doing two hand movement sequences (verbal-motor interaction), the MBPT (where counting interferes with the recall of letters), and the Grooved Pegboard completed at the same time as a concomitant task (where doing one distractor task with one hand should interfere with the task done by the other hand, i.e. a motor-motor interaction). However, results did not support this hypothesis. There was only a trend for increased performance on the CVLT-II immediate free recall following 1 g/kg of glucose.

Participants' comments during testing indicated that overall, they found the CVLT-II and the MBPT challenging but not the Grooved Pegboard. However, no significant results were obtained on the MBPT 36 seconds aside from an age effect. It was therefore hypothesized that although groups were performing similarly on the main task, there might have been differences on the secondary tasks. Although performance on the concomitant task of the CVLT-II was not measured, the total number of correct subtractions completed during the MBPT, for both the 9 and 36 second delay, as well as the total number of nuts that had been screwed onto bolts during the secondary task of the Grooved Pegboard, for both dominant and non-dominant hands, could be analyzed. However, Wilks' Lambda multivariate analyses revealed no significant impact of solution ($F(2, 90) = 0.05, p = .95$), glucose dose ($F(4, 180) = 0.72, p = .58$), glucoregulation ($F(2, 90) = 0.03, p = .97$) or age ($F(2, 90) = 2.18, p = .12$) on the interference of the MBPT and all the interactions were non-significant ($p > .05$). Similar results were obtained for performance on the concomitant task of the Grooved Pegboard with Wilks' Lambda mutlivariate analyses failing to reach significance for solution ($F(2, 90) = 0.67, p = .52$), glucose dose ($F(4, 180) = 1.63, p = .17$), glucoregulation ($F(2, 90) = 2.43, p = .09$) and age ($F(2, 90) = 0.56, p = .57$), as well as for all the interactions ($p > .05$). In summary, there were no differences in costs on the secondary task of the MBPT or the Grooved Pegboard that could explain the comparable performance on the main task between groups. Our present results do not support the idea that glucose effects are more easily seen in situations or task combinations that require more effort; on the other hand, the general lack of effect of glucose on cognition may be related to a sub-optimal dose which would make the test of the role of increased effort less powerful in the present study (i.e., we might not see the differential impact on task difficulty because our glucose doses were not appropriate).

Glucoregulation

This study also examined whether glucoregulation mediated the impact of glucose on neuropsychological performance and whether age interacted with the impact of glucoregulation on cognition. Previous research has shown that type 2 diabetes is associated with cognitive impairments (Brands, Van den Berg et al., 2007; Cukierman-Yaffee, 2009; Ebady et al., 2008; Elderkin-Thompson et al., 2009; Kodl & Seaquist, 2008; R. Kumar et al., 2008; Manschot et al., 2008; Okereke et al., 2008; Paile-Hyvarinen et al., 2009; Ruis et al., 2009; Saczynski et al., 2008; Tiehuis, Vincken et al., 2008; van den Berg et al., 2008; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009; Yeung et al., 2009) and that the decline in cognitive performance is more pronounced in older adults (Awad, Gagnon et al., 2004; Biessels et al., 2008; Roriz-Filho et al., 2009; Ryan & Geckle, 2000). Additionally, decreased performance on neuropsychological testing has been demonstrated in older adults with impaired or altered glucose regulation (Convit et al., 2003; Hiltunen et al., 2001; Kalmijn et al., 1995; Kaplan et al., 2000; Lamport et al., 2009; Messier et al., 1997; Messier et al., 2003; Vanhanen et al., 1998). The cognitive domains that appear to be more vulnerable to the impact of poorer glucose regulation are attention, working memory and verbal memory. A study, using a similar design as the present one, examined the interaction between age, glucoregulation and solution (glucose or saccharin) on cognitive performance (Messier et al., 2003). Older worse regulators showed significantly more deficits on cognitive tasks (Arithmetic, Digit span Forward and Backward, Spatial Span Forward, Letter-Number Sequencing, Symbol Search, Logical Memory and Modified Brown-Peterson task) after saccharin ingestion but the ingestion of glucose appeared to reduce the gap in performance between this group and younger better and worse regulators as well as older better regulators.

On the basis of these results, we had hypothesized that older adults categorized as worse regulators would perform more poorly on the cognitive tasks compared to better regulators and that glucose facilitation would be more observable in older adults who regulate glucose more poorly. Results obtained in the present study indicated no statistically significant impact of glucoregulation on cognitive performance, irrespective of age group. However, several trends were noted. Better regulators recalled more consonants on the MBPT 9 seconds than worse regulators. This is consistent with results obtained in a study using the same task but with a 20-second delay with older participants categorized as worse regulators (mean age = 76.2) obtaining lower scores on this task compared to older participants with better glucoregulation (mean age = 79.0) (Messier et al., 2003).

In the present study, we also found that worse regulators in the 1 g/kg group had better CVLT-II recognition hits score in the glucose condition than in the saccharin condition. Furthermore, better regulators in the 1 g/kg group completed the Grooved Pegboard task more quickly compared to worse regulators in the glucose condition. Also in line with the hypothesis, younger worse regulators obtained higher scores on the Spatial Span Forward compared to older worse regulators. Finally, older worse regulators took more time to complete the Grooved Pegboard task compared to younger worse regulators.

Mixed results were obtained on the Spatial Span Backward in that some of the results were in keeping with the a priori hypotheses whereas others were not. Results that are consistent with the hypothesis are: younger better regulators outperformed the older better regulators on the Spatial Span Backward in both drinking conditions, younger worse regulators obtained higher scores compared to older worse regulators following glucose ingestion, and younger worse regulators performed better on this task following glucose ingestion compared to when they received saccharin. However, several results on this measure are not in line with the hypothesis: older better regulators performed more poorly compared to older worse regulators in the saccharin condition, younger better regulators obtained lower scores than younger worse regulators following glucose ingestion, and older worse regulators recalled more sequences in the saccharin condition than in the glucose condition. Furthermore, results on the Digit Span Forward contradicted the hypothesis since older worse regulators recalled more number sequences compared to older better regulators in the saccharin condition. Notwithstanding the few significant results, Table 17 shows that better regulators, particularly older ones, achieved a better performance on more tasks even though this advantage was minimal in some tests.

A number of factors may have contributed to the small impact of glucoregulation on cognition in the present study. First, although the age range of participants was fairly large (60 - 85), 65% of participants were between 60 and 69 years of age (younger better regulators: mean age = 63.50; younger worse regulators: mean age = 63.26; older better regulators: mean age = 72.91; older worse regulators: mean age = 74.46). It is obvious that the age distribution in the present study differs from the Messier et al. (2003) study (younger better regulators: mean age = 64.70; younger worse regulators: mean age = 68.25; older better regulators: mean age = 79.00; older worse regulators: mean age = 76.20) that showed an interaction between glucoregulation and age. It is possible that the overall younger age of our participants precluded the detection of glucoregulatory effects. This is consistent with what is observed in type 2 diabetes where the greatest deficits are found in patients older than 65 years (Ryan & Geckle, 2000).

Secondly, the method used to measure glucose regulation in the present study could also have biased the evaluation of glucoregulatory status. It is important to mention that in this study, blood glucose was only measured once at each time point (i.e., fasting level, 30 minutes after drinking the sweet solution containing either glucose or saccharin and 120 minutes following ingestion of the sweet solution). Since factors such as stress can affect blood glucose levels (Wing, Epstein, Blair, & Nowalk, 1985), measurements might have been more accurate if several readings were taken at each time point to obtain an overall mean. It is possible that using three different glucose doses to evaluate glucoregulation increased the variability in the categorization of participants as better or worse regulators compared to the use of a single glucose dose as was done in previous studies (Kaplan et al., 2000; Messier et al., 1997; Messier et al., 2003). However, people with worse glucose regulation typically have blood glucose peaks that are high. The problem resides with participants who are in the middle since those in the extreme ranges are most likely categorized correctly.

It would have been useful to divide participants into three groups, i.e. those with better glucose regulation, those in the middle and participants with worse glucose regulation but this was unpractical because of a sharp decrease in statistical power to perform the relevant comparisons. Therefore, we used a median split to divide participants into better and worse regulators which meant that a number of participants in the middle group could have belonged to either one of higher or lower groups. Hence, using a median split led to a decreased discrimination between higher or lower glucoregulatory groups.

For curiosity's sake, we examined whether participants in the middle were masking significant results and reanalyzed the data using the top and bottom 33% of the measure used to determine the glucoregulation index (acknowledging that the statistical power was much lower for this analysis and that it was impractical to do this for each neuropsychological test). First, this was done using the median split of the recovery index for each glucose dose group (n = 22 for each glucose dose group; better regulators: n = 33, worse regulators: n = 33; younger: n = 31, older: n = 35). However, Wilks' Lambda multivariate analyses revealed no significant impact of glucoregulation ($F(19, 36) = 1.03, p = .46$) and none of the interactions were significant (glucoregulation and age: $F(19, 36) = 0.65, p = .84$; glucoregulation and glucose dose: $F(38, 72) = 0.89, p = .65$; glucoregulation, age and glucose dose: $F(38, 72) = 0.81, p = .76$; glucoregulation and solution: $F(19, 36) = 0.84, p = .65$; glucoregulation, solution and age: $F(19, 36) = 0.95, p = .53$; glucoregulation, solution and glucose dose: $F(38, 72) = 1.02, p = .46$; glucoregulation, solution, age and glucose dose:

F(38, 72) = 0.78, *p* = .80). Secondly, the analysis was also done using instead the distribution of *z* scores to categorize participants (300 mg/kg: n = 18, 650 mg/kg: n = 28, 1 g/kg: n = 22; better regulators: n = 34, worse regulators: n = 34; younger: n = 37, older: n = 31) since the recovery index differs according to the glucose dose administered (larger glucose doses produced higher glucose levels). Similarly, Wilks' Lambda multivariate analysis was non-significant for glucoregulation (*F*(19, 38) = 1.15, *p* = .35) and none of the interactions reached significance (glucoregulation and age: *F*(19, 38) = 0.82, *p* = .67; glucoregulation and glucose dose: *F*(38, 76) = 0.83, *p* = .73; glucoregulation, age and glucose dose: *F*(38, 76) = 0.81, *p* = .76; glucoregulation and solution: *F*(19, 38) = 0.70, *p* = .79; glucoregulation, solution and age: *F*(19, 38) = 0.84, *p* = .65; glucoregulation, solution and glucose dose: *F*(38, 76) = 0.78, *p* = .80; glucoregulation, solution, age and glucose dose: *F*(38, 76) = 0.64, *p* = .94). These supplementary analyses suggest that the absence of an overall large effect of glucoregulation was unlikely to be due to the inclusion of people with normal recovery indexes (i.e., the group of people close to the median) in the two glucoregulatory groups.

Strengths and limitations

This study has several strengths, notably the utilization of a relatively large sample (n = 103) compared to previous research on glucose and cognitive performance. A total of 79% of the studies reviewed in Appendices A and B had a sample of 75 or less, with 35% of these studies having 25 or less participants. Furthermore, a counterbalanced sequence was used for the administration of the drinking solutions and of the original/alternate forms to control for order effects. Additionally, steps were taken to ensure that participants were blind to the solution ingested. Finally, a variety of cognitive measures were included in the battery of tests. Although previous research has mostly focused on examining the impact of ingested glucose on measures of verbal episodic memory, studies have also shown that glucose can enhance visual memory (Metzger, 2000; Metzger & Flint, 2003; Sunram-Lea et al., 2001, 2002a, 2002b), kinaesthetic memory (Scholey & Fowles, 2002) as well as other cognitive domains such as attention (Hall et al., 1989; Kennedy & Scholey, 2000; Scholey et al., 2001; Sunram-Lea et al., 2002b), working memory (Martin & Benton, 1999), word list generation (Donohoe & Benton, 1999; Riby et al., 2006), and visuospatial ability (Donohoe & Benton, 1999). Therefore, to gain a better understanding of the possible effect of glucose on cognitive performance, a more comprehensive battery of tests was used.

An important limitation of this study is that the sample was highly educated ($M = 15.49$, $SE = 0.30$), with a high level of estimated intellectual functioning based on performance on the WTAR ($M = 115.89$, $SE = 0.83$). Therefore, it is possible that given the overall higher level of intellectual functioning of this sample of participants, the cognitive tasks were less challenging and hence, did not stretch cognitive capacity sufficiently to observe impairments or improvements. More difficult tasks might have resulted in greater marked deficits thus creating a margin for improvement. It is also possible that worse glucose regulation would have resulted in more pronounced cognitive deficits in a sample with a lower level of estimated intellectual functioning. Furthermore, practice effects were observed on 11 out of 19 cognitive variables, which may have increased variability. Glucoregulatory status was only measured once during testing using a non-standard measure (as opposed to an oral glucose tolerance test) with participants receiving different doses of glucose. Furthermore, the differentiation between better and worse glucoregulators was based on the sample obtained in this study. A high proportion of participants were between 60 and 69 years of age which led to a positively skewed distribution ($z_{\text{skewness}} = 3.44$) with a lesser number of very old participants which would be expected to show the greatest impact of glucoregulation and glucose on cognition thus limiting the ability of the present experiment to compare adequately oldest old with younger old to examine the possible interaction between glucoregulation and age. Finally, we could have tested more people given that the interaction between the three independent between-subject variables (glucose dose, glucoregulation and age) resulted in a small number of participants per group and that the inclusion of a larger group of participants could have allowed three glucoregulatory groups.

Future perspectives

More research needs to be done on the glucose facilitation effect and task difficulty by manipulating task difficulty directly by comparing performance in both single and dual task conditions. Although this was not specifically addressed in this study, several studies conducted in younger adults have shown that this might be a crucial factor to observe glucose enhancement of cognitive performance (Donohoe & Benton, 1999; Foster et al., 1998; Kennedy & Scholey, 2000; Scholey et al., 2009; Sunram-Lea et al., 2002b).

The optimal dose(s) of glucose (adjusted to body weight) remains to be established. As mentioned previously, very few studies in humans have compared doses of glucose adjusted to body weight, (Flint & Turek, 2003; Messier et al., 1998), and only one study in older adults compared three doses of glucose and these were not adjusted to body weight (Parsons & Gold, 1992). Although the animal literature only uses doses adjusted to weight (Durkin et al., 1992; Greenwood & Winocur, 2001; Hughes, 2006; Hughes & Neeson, 2003; Jafari et al., 2004; Kopf, Buchholzer, Hilgert, Loffelholz, & Klein, 2001; McNay et al., 2000; McNay & Gold, 2001; Means & Fernandez, 1992; Messier, Durkin, Mrabet, & Destrade, 1990; Ragozzino, Arankowsky-Sandoval, & Gold, 1994; Ragozzino & Gold, 1991; Ragozzino, Parker, & Gold, 1992; Ragozzino et al., 1996; Ragozzino, Wenk, & Gold, 1994; Rashidy-Pour, 2001; Salinas & Gold, 2005; Schroeder & Packard, 2003; Talley et al., 2002), research conducted in humans has generally used absolute doses of glucose (see Appendices A and B) even though a dose-response curve has been clearly demonstrated in animal studies. The presence of a dose-response effect in both animals and humans raises a number of questions regarding the mechanisms of action of glucose on cognitive processes. There seems to be optimal doses at which glucose improves cognition but higher or lower doses do not produce a facilitative effect. The relative absence of effect of larger doses suggests that glucose action on the brain is not merely an effect of increasing supply to the brain through increased transport of glucose from blood to brain although the additional mechanism that underlays the dose-response curve has not been identified.

Finally, more research needs to be done examining the impact of glucoregulation on cognitive performance using imaging techniques to determine whether regions other than the hippocampus have atrophy. Only one study has been conducted to date showing a relationship between worse glucose regulation, decreased hippocampal volume and poorer performance on a measure of verbal episodic memory in middle-age and older participants (Convit et al., 2003). The combination of neuropsychological testing and imaging techniques could address why worse glucose regulation results in lower performance on cognitive tasks. Future research will therefore need to investigate whether certain brain regions are atrophied and if there is an association between imaging findings and scores obtained on neuropsychological tasks. Although the mechanisms underlying the association between diabetes and cognitive decline likely include multiple factors, new research shows that dysregulation of the hypothalamic-pituitary-adrenal axis resulting in increased cortisol levels (Bruehl et al., 2007) or reduced brain-derived neurotrophic factor may underlay diabetes cognitive deficits (Arentoft et al., 2009). It remains to be determined whether these abnormalities are also present in people with altered glucose regulation who do not meet criteria for diabetes. Since marked cognitive impairments appear to be mostly observable in older adults with type 2 diabetes or older adults with impaired glucose tolerance/altered glucose regulation, research focusing on people aged 75 years and over might be more revealing.

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Appendix A

Performance of young adults on cognitive tests following glucose ingestion

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/ group
Awad et al. (2002)	74	21.00	50 g	Yes	Logical memory	No
					Verbal free recall	No
					Order reconstruction recall	Yes (poor regulators)
Azari (1991)	18	21.00	30 g, 100 g	No	Word list	No
Benton & Owens (1993)	Experiment 1					
	153	21.70	50 g	No	Word list	No (but participants with increased blood glucose levels recalled more words)
					Spatial memory test	No
	Experiment 2					
	53	21.50	50 g + 25 g + 25 g	No	Story recall	No
					Word list	No (but significant correlation between amount of words recalled and blood glucose levels)

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
Benton et al. (1994)	Experiment 1					
	70	21.46	50 g + 25 g	No	Rapid information processing	No (but participants with increasing blood glucose levels had faster reaction times)
					Word list	Yes
	Experiment 2					
	50	21.70	50 g + 25 g	No	Stroop test	No (but participants with increasing blood glucose levels were faster)
Craft et al. (1994)	27	20.80	50 g	Yes	Paragraph recall	Yes (men-poor)
					Modified CVLT	No
					Pattern recall & recognition	No
					Serial reaction time task	No
					Paced serial addition test	No
					Verbal fluency	No
					Stroop test	No
Donohoe & Benton (1999)	Experiment 1					
	67	21.80	50 g	No	Water jars test	No
					Embedded figures test	No
					Logical reasoning test	No
	Experiment 2					
	69	20.20	50 g	No	Verbal fluency	Yes

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
					Block design test	No (but participants with falling blood glucose levels were significantly faster)
					Porteus maze	Yes
Flint & Turek (2003)	67	19.49	10 mg/kg, 100mg/kg, 500 mg/kg or 50 g	No	Test of variables of attention	No
Ford et al. (2002)	20	20-23	25 g	No	Word recall	No
					Word recognition	No
Foster et al. (1998)	30	19.50	25 g	No	CVLT + motor sequences	Yes
					Rey-Osterrieth figure	No
					Digit span	No
Hall et al. (1989)	12	20.00	50 g	Yes	Paired-associates (easy)	No
					Paired-associates (hard)	No
					Logical memory	No
					Digit span forward	Yes (no difference between good and poor regulators)
					Digit span backward	No
					Visual memory	No

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
Kennedy & Scholey (2000)	20	20.40	25 g	No	Serial sevens	Yes
					Serial threes	No
					Word retrieval	No
Martin & Benton (1999)	80	22.60	50 g	No	Consonant trigrams	Yes
Meikle et al. (2004)	Younger					
	14	21.80	25 g, 50 g	Yes	Memory search	No
					Visual search	No
					Trail A	No
					Trail B	No
					Letter cancellation	No
					FAS	No
					Word recall	Yes (both doses, no difference between good and poor regulators)
	Middle-aged					
	11	38.4	25 g, 50 g	Yes	Memory search	Yes (both doses, no difference between good and poor regulators)
					Visual search	No
					Trail A	No
					Trail B	No
					Letter cancellation	No

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
					FAS	No
					Word recall	Yes (both doses, no difference between good and poor regulators)
Meikle et al. (2005)	<u>Experiment 1</u>					
	37	28.30	25 g	No	Word pairs-cued recall (low and high imagery)	Yes (low imagery)
	<u>Experiment 2</u>					
	24	18.90	25 g	No	Word lists (phonologically similar and dissimilar words; various list lengths)	Yes (longer lists)
Messier et al. (1999)	36	21.30	50 g	Yes	Verbal free recall	Yes (poor regulators)
Messier et al. (1998)	100	21.3	10, 100, 300, 500, 800, or 1000 mg/kg	No	Word lists	Yes (300mg/kg-increase in primacy effect)
Metzger (2000)	34	21.1	50 g	No	Facial recognition task	Yes
Metzger & Flint (2003)	18	23.5	50 g	No	Facial recognition task	Yes

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
Owens & Benton (1994)	96	21.2	50 g	No	Inspection time	No
					Reaction time	No (but participants with increasing blood glucose levels were significantly faster)
Parker & Benton (1995)	100	20.15	50 g + 25 g	No	Dichotic listening-recall	Yes (right ear)
					Dichotic listening-recognition	No
Riby et al. (2006)	14	30.10	25 g	No	Paired associates-single task	Yes
					Paired associates-dual task	No
					Word lists-concrete	No
					Word lists-abstract	No
					Letter fluency	No
					Category fluency	Yes
Scholey et al. (2001)	20	22.70	25 g	No	Serial sevens	Yes
					Verbal fluency	No
					Word lists	No
Scholey et al. (2009)	120	21.60	25 g	No	Word recognition-single task	No
					Word recognition-dual task	Yes (but only on tracking task, not on memory)

Study	n	Age	Dose(s)	Divided into good and poor glucoregulators	Cognitive tests	Improvement in performance compared to control condition/group
Scholey & Fowles (2002)	45	22.58	25 g	No	Maze test	Yes
Sunram-Lea et al. (2001)	60	21.00	25 g	No	CVLT + motor sequences Rey-Osterrieth figure recall Digit span	Yes Yes No
Sunram-Lea et al. (2002a)	60	21	25 g	No	CVLT + motor sequences Rey-Osterrieth figure recall Serial sevens	Yes (delayed recall) Yes (delayed recall) No
Sunram-Lea et al. (2002b)	80	20.00	25 g	No	CVLT + interference task (motor sequences or computer task or none) Rey-Osterrieth figure recall Serial sevens	Yes (interference) Yes Yes
Sunram-Lea et al. (2004)	40	21.00	25 g	No	CVLT + motor sequences Rey-Osterrieth figure recall Serial sevens	Yes No No
Sunram-Lea et al. (2008)	56	20.00	25 g	Yes	Word recognition (hits, remember and know (i.e., familiar))	Yes (hits and remember responses but not know)

Note: CVLT = California Verbal Learning Test

Appendix B

Performance of older adults with impaired glucose tolerance (IGT)/poor glucose regulation compared to normoglycemic (NGT)/good glucose regulators on cognitive tests

Study	n	Age	Cognitive tests	Results: IGT/poor regulators compared to NGT/good regulators	Drink ingestion	Cognitive process(es) showing improvement in IGT/poor regulators
Convit et al. (2003)	30	68.6	Immediate & delayed Wechsler paragraph recall MMSE	Lower scores Lower scores	n/a	n/a
Hiltunen et al. (2001)	43	>70	MMSE	Lower scores	n/a	n/a
Kalmijn et al. (1995)	47	77	MMSE	Lower scores	n/a	n/a
Kaplan et al. (2000)	20	72.3	Word lists Immediate & delayed paragraph recall Trails B Attention task	Lower scores Lower scores Lower scores No difference	50 g glucose saccharin	Improvements on tasks of memory and divided attention following glucose ingestion
Lindeman et al. (2001)	175	74.6	MMSE Pentagon drawing Digits forward Fuld object memory Clock drawing	No difference Higher scores No difference No difference No difference	n/a	n/a

Study	n	Age	Cognitive tests	Results: IGT/poor regulators compared to NGT/good regulators	Drink ingestion	Cognitive process(es) showing improvement in IGT/poor regulators
			Trails (color)	No difference		
Messier et al. (1997)	15	62.3	Logical memory	Lower scores (men)	50 g glucose saccharin	Improvements on some tasks of attention and memory following glucose ingestion
			Digit span	Lower scores on backward (men)		
			Visual memory span	No difference		
			Verbal paired associates	No difference		
			Digit symbol test	No difference		
			Cancellation H test	No difference		
			Word lists	Lower scores (men)		
Messier et al. (2003)	Younger					
	28	66.4	Arithmetic	Lower scores (older)	50 g glucose saccharin	Improvements on tasks of attention/working memory following glucose ingestion
	Older		Digit span forward	Lower scores (older)		
	29	77.6	Digit span backward	Lower scores (both)		
			Spatial span forward	Lower scores (older)		
			Spatial span backward	No difference		
			Letter-number sequencing	Lower scores (both)		
			Digit-symbol coding	No difference		
			Symbol search	Lower scores (older)		
			Verbal free recall	No difference		
			Order reconstruction recall	No difference		
			Logical memory	Lower scores (older)		
			Modified Brown-Peterson	Lower scores (older)		

Study	n	Age	Cognitive tests	Cognitive process(es) showing improvement in IGT/poor regulators participants	Drink ingestion	Cognitive process(es) showing improvement in IGT/poor regulators
Vanhanen et al. (1998)	80	72.9	MMSE Buschke selective reminding test Russell's adaptation of the visual retention test Trails Verbal fluency	Lower scores Lower scores on long-term recall No difference No difference No difference	n/a	n/a

Appendix C

Impact of normalizing glucose levels on cognition in older adults with type 2 diabetes

Study	n	Age	Treatment	Cognitive domains assessed	Improvement in performance
Gradman et al. (1993)	30	68	Glipizide	Learning & memory	Yes
				Attention	No
				Complex & simple perceptual motor functions	No
Meneilly et al. (1993)	16	71	Oral hypoglycemic medications	Mental status	No
				Psychomotor speed	No
				Attention & concentration	On some tasks
				Learning & memory	Yes
				Problem solving	Yes
Mussell et al. (2004)	26	-----	Oral hypoglycemic medications alone or in combination with insulin	Verbal fluency	No
				Learning & memory	No
				Attention & concentration	Yes (comparable to controls)
				Psychomotor speed	Yes (comparable to controls)
Naor et al. (1997)	20	63.6	Intensive treatment : Oral anti-diabetic drug, adapted diet & daily monitoring of blood glucose	Reaction time	No
				Concentration	Yes
				Psychomotor speed	Yes
	20	63.8	Regular treatment: Oral anti-diabetic drug & diet	Reaction time	No
				Concentration	No
				Psychomotor speed	No

Study	n	Age	Treatment	Cognitive domains assessed	Improvement in performance
Ryan et al. (2006)	69	60.7	Metformin & Rosiglitazone	Working memory	Yes
				Learning & memory	No
				Reaction time	No
	72	59.6	Metformin & Glyburide	Working memory	Yes
				Learning & memory	No
				Reaction time	No
Wu et al. (2003)	≤5years		Oral hypoglycemic agent alone or in combination with insulin/another hypoglycemic agent	Cognitive screening	Yes (less decline in treated)
	Treated			Learning & memory	No
	119	70.6			
	Not treated				
	262	70.6			
	>5years		Oral hypoglycemic agent alone or in combination with insulin/another hypoglycemic agent	Cognitive screening	Yes (less decline in treated)
	Treated			Learning & memory	No
	222	70.6			
	Not treated				
	115	69.8			

Appendix D

Ethics approval

Université d'Ottawa | University of Ottawa
Service de subventions de recherche et déontologie | Research Grants and Ethics Services

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

ATTESTATION D'APPROBATION ÉTHIQUE

La présente attestation certifie que le Comité d'éthique de la recherche en Sciences de la Santé et Sciences de l'Université d'Ottawa a examiné la demande d'approbation éthique pour le projet de recherche **Effect of various doses of glucose on cognition in older adults (dossier H 02-06-03)** présentée par Dr Claude Messier et Dre Michèle Gagnon. Valérie Mertens, étudiante et assistante de recherche, utilisera peut-être les données pour sa thèse. Le Comité d'éthique a déterminé que la demande respectait les principes éthiques établis par l'Énoncé de politique des trois conseils et par les règles de procédure des Comités d'éthique de l'Université d'Ottawa. Le Comité d'éthique a donc accordé une catégorie 1a (approbation) à ce projet. La présente attestation est valide pour un an à partir de la date indiquée ci-dessous.

Rita D'Alessandro
Responsable de l'éthique en recherche
Pour Dr Daniel Lagarec, Président du CÉR en
Sciences de la Santé et Sciences

4 avril 2006
Date

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(613) 562-5841 • Téléc/Fax (613) 562-5338
http://www.uottawa.ca/services/research/[illegible]/index.html

Appendix E

Advertisement to recruit participants

PEOPLE 60 YEARS AND OLDER NEEDED FOR A STUDY ON MEMORY

Dr. Claude Messier and his collaborator at the University of Ottawa and the Institute of Mental Health Research (Royal Ottawa Hospital) are looking for healthy people aged 60 years and older to study the effects of ingested glucose on memory.

Volunteers for this important study should be:

- available for 2 ½ hour morning visits
- able to come to the University of Ottawa for 2 visits

Volunteers should not:

- be diabetic
- have suffered from a brain disorder in the past
- have had loss of consciousness for more than one hour
- be currently treated for depression
- be consulting a psychiatrist
- suffer from hypoglycemia or metabolic diseases rendering fasting dangerous
- have hepatitis
- suffer from dementia
- suffer from alcohol or drug abuse
- be colour-blind

Parking expenses will be reimbursed. For more information, please call:
Valérie Mertens, Research Coordinator
Tel. 562-5800 extension 4185
At the end of the study, you will receive $20 for your participation.

Appendix F

Screening interview

“Hello. My name is Valérie Mertens. I’m calling from the University of Ottawa concerning the study on memory. I believe you left a message that you might be interested in participating in the study? Would you like to know a little bit about the study? Is this a good time for you?”

“Your participation will consist essentially of coming fasted (no eating or drinking (except water) after midnight preceding each of the visits) for 2 sessions at the University of Ottawa lasting approximately two hours and a half during which you will be asked to undergo mental performance tests after drinking a sweet solution containing either glucose (sugar) or saccharin and answering questions related to your lifestyle (exercise, smoking, etc.) and mood. At the time of the test, you will not be made aware of which solution you drink and the dose of glucose. However, at the completion of the second test session, you will be told so. To participate in this study, you must be proficient in English. You will also be asked to give a small drop of blood three times during each session to measure your blood sugar levels. Blood will be obtained through a small pin prick (measured using a portable glucose meter). At the end of the study, you would receive $20.00 for participating. Also, if you come to the university by car, we pay for your parking. So how does that sound?”

If Interested in participating:

“I would now have to ask you a few questions to determine if you are eligible to participate in the study. Certain criteria have been established for the study. Based on these criteria, I’ll be asking you questions to determine if you are eligible to participate in the study. Your answers are strictly confidential and they would be destroyed immediately if you did not participate in the study.”

What is your age? (Age has to be ≥60) Age = _____ Gender = _____ (male=0; female=1)

Yes = 1 No = 0

Medical History

1- Are you diabetic? ________________________________ /__/

2- Do you suffer from chronic hypoglycemia? ________________________________ /__/

3- Do you often feel very weak if you do not eat?________________________________ /__/

4- Have you ever had a brain hemorrhage (intracranial) or stroke? ________________ /__/

5- Have you ever had a brain tumor or lesion or head injury? ________________ /__/

6- Have you ever had any brain disease? ________________________________ /__/

7- Do you have chronic hepatitis? ________________________________ /__/

8- Do you have high blood pressure requiring medication? ________________ /__/

9- Have you ever had loss of consciousness for more than one hour? ______________ /__/

10- Have you ever experienced a sudden: 1) weakness or numbness of the face, arm or leg; 2) dimness or loss of sight, especially in one eye; 3) difficulty with speaking or loss of speech?
____ /_/

11- How many alcoholic drinks did you take in the last week? ______________ /_/

12- How many alcoholic drinks did you take in the last month? ______________ /_/

13- Would you know how many alcoholic drinks it takes you to be intoxicated? ______ /_/

In terms of alcohol, what is it that usually drink?
Do you get intoxicated every time you drink?
Could you stop drinking if you wanted to?

14- Do you take recreational drugs apart from cannabis? ________________ /_/

15- Have you used cannabis on a daily basis in the last month? ______________ /_/

16- Do you take any prescription drugs? __________________________ /_/

____

17- Are you seeing a psychiatrist presently? _______________________ /_/

18- Are you currently being treated for depression? ___________________ /_/

19- Do these 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 _____________________ /_/

20- Are you colour-blind? __________________________ /_/

21- When did you have your last medical checkup? ___________________ /_/

Now I would like to ask you a few questions on your memory. Yes=1; No=0

1) Do you have memory problems? ________________________ /_/

2) Do you have difficulty remembering the names of persons that have been introduced to you? ____________________________ /_/

3) Do you misplace objects _____________________________ /_/

4) Do you have difficulty remembering a list of things to buy or a list of things to do? __ /_/

5) Do you have problems remembering telephone numbers or postal codes? ________ /_/

6) Does it often take you a long time to remember information ______________ /_/

7) Does distraction (e.g. noise, another person talking) make it harder for you to remember information? ___________________________ /_/

8) If you are experiencing some memory problems, would you say, they came suddenly or their appearance was over a long period?

(gradual=0; sudden=1) ________________________ /_/

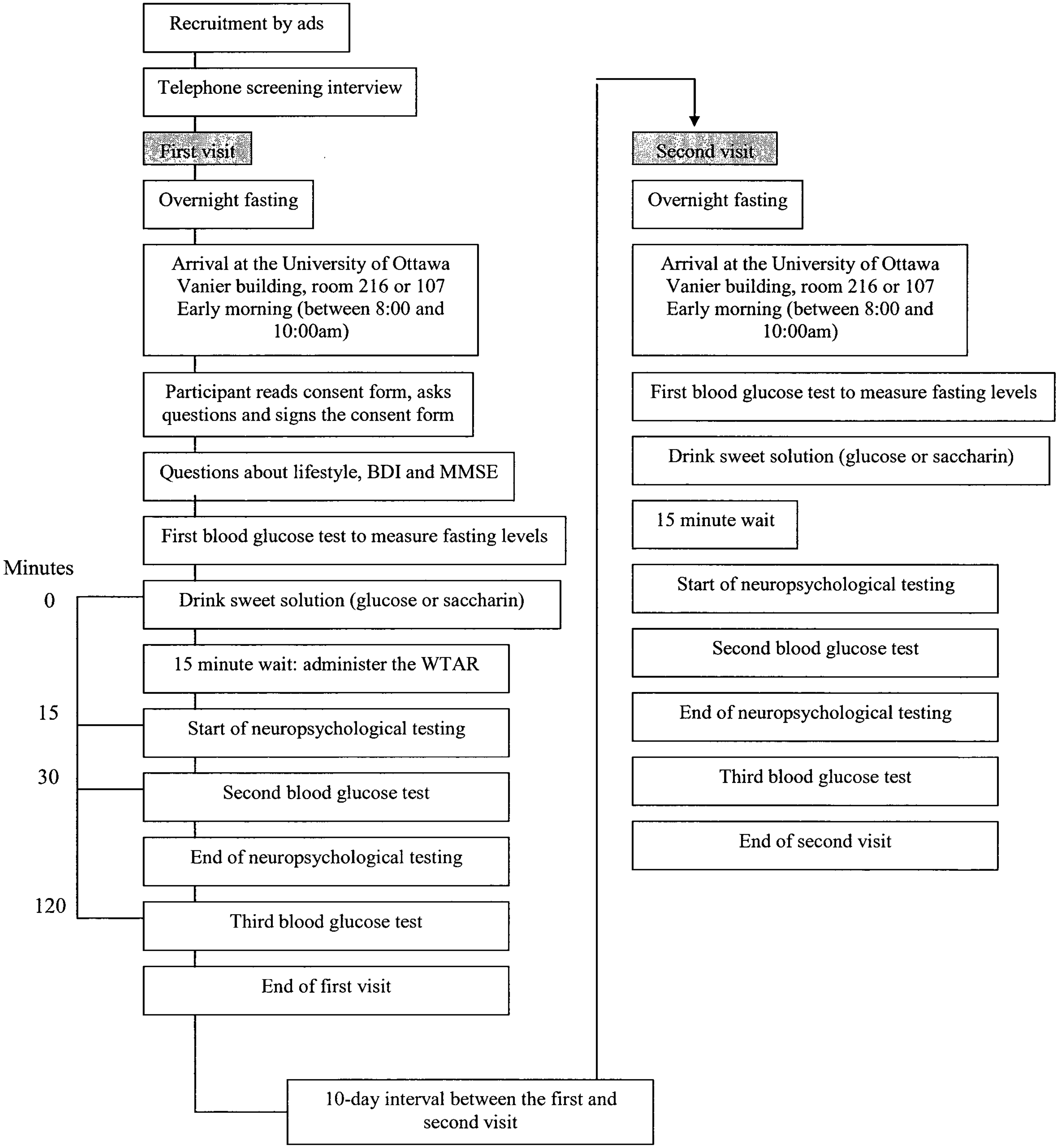
Statement 1: You appear to have met the criteria for our study and we would be glad if you could participate.

During the first visit, you will be asked to complete two questionnaires (Mini-Mental State Examination and the Beck Depression Inventory-II) that will be used to further determine your eligibility to participate in this study. If you do not meet the criteria that have been established for this study, you will be excluded from the study.

Statement 2: Unfortunately, because you have (had) ______and this is one of the criteria, we will not be able to include you in this study. Thank you very much for your time.

Appendix G

Overall timeline of the study



Appendix H

Consent form

Title of the Study: Effect of various doses of glucose on cognition in older adults

Name of Researchers: Dr. Claude Messier, School of Psychology, University of Ottawa, (613)562-5800 ext 4562, cmessier@uottawa.ca and Dr. Michèle Gagnon, Institute of Mental Health Research, Royal Ottawa Hospital, (613)722-6521 ext 7030, mgagnon@rohcg.on.ca. The research assistants, Valérie Mertens, Delyana Miller or Rebecca Ryan, School of Psychology, University of Otttawa, (613)562-5800, ext 4301, might use the results of this study for their theses.

Invitation to Participate: I am invited to participate in the abovementioned research study conducted by Dr. Claude Messier and Dr. Michèle Gagnon.

Purpose of the Study: I understand that the purpose of the study is to measure the effect of different doses of glucose that will be adjusted according to weight on memory and mental activity. The researchers also want to examine the impact of drinking a glucose solution when I am performing two tasks at the same time. Finally, they want to see if the speed at which my body assimilates glucose is linked to performance on mental activity tasks.

Participation: My participation will consist essentially of coming fasted (no eating or drinking (except water) after midnight preceding each of the visits) for 2 sessions at the University of Ottawa lasting approximately two hours and a half during which I will be asked to undergo mental performance tests after drinking a sweet solution containing either glucose (sugar) or saccharin and answering questions related to my lifestyle (exercise, smoking, etc.) and mood. At the time of the test, I will not be made aware of which solution I drink and the dose of glucose. However, at the completion of the second test session, I will be told so. To participate in this study, I must be proficient in English. During the first visit, I will be asked to complete two questionnaires (Mini-Mental State Examination and the Beck Depression Inventory-II) that will be used to determine if I am eligible to participate in this study. I understand that if I do not meet the criteria that have been established for this study, I will be excluded from the study.

The sessions have been scheduled for (date) and will take place at the University of Ottawa, Vanier Building, room 216.
1) ________________________________
2) ________________________________

I will also be asked to give a small drop of blood three times during each session to measure my blood glucose levels. Blood will be obtained from the fingertip using a small pin prick and will be placed on a testing strip. The pin and test strip used will be disposed in a sharps container. I will be told if my blood glucose is too high; in that case, I will be advised to consult my doctor to evaluate if I need medical attention.

Risks: I understand that since my participation in this study entails fasting for some period of time, it may cause me to feel faint. I may also feel some pain associated with the pin prick to obtain blood. I may also feel tired after the mental tests. I will also have received assurance from the researcher that every effort will be made to minimize these risks. Fruit juice, soft drinks or some food will be available to me if I request them in case I feel too faint to continue the experiment. A device is used to produce the pin prick that minimizes pain. I will be allowed to rest whenever I require it during the mental activity tests.

Benefits: My participation in this study will not benefit me directly in any way except that I will be told if my blood glucose levels are too high. My participation to this experiment will further knowledge on the role of ingested glucose on cognition.

Confidentiality: I have received assurance from the researcher that the information I will share will remain strictly confidential. I understand that the contents will be used only for research purposes and that my confidentiality will be protected by rendering all the information anonymous after I complete the experiment.

Anonymity: Anonymity will be protected in the following manner in that my results will remain anonymous and my personal information and results will not be communicated in any way except as part of group averages.

Conservation of Data: The data collected (blood glucose data, results at mental activity tests, answers to questionnaires) will be kept in a secure manner in a locked room at the University of Ottawa. The numeral key identifying my results will be kept in a locked cabinet during my participation to the study and will be destroyed at the end of my participation. The cabinet will be accessible only to the researchers and the research assistant named above.

Compensation: I will receive $20.00 for my participation in this study. In addition, my parking expenses will be reimbursed.

Voluntary Participation: I am under no obligation to participate and if I choose to participate, I may withdraw from the study at any time and/or refuse to answer any questions. If I choose to withdraw, all data gathered until the time of withdrawal will be made anonymous but may be used by the researchers if needed.

Acceptance: I, *(___________________________________),* agree to participate in the above research study conducted by Dr. Claude Messier and Dr. Michèle Gagnon of the School of Psychology, University of Ottawa. I understand that by accepting to participate I am in no way waiving my right to withdraw from the study.

If I have any questions about the study, I may contact the researchers or the research assistant at the numbers mentioned above.

If I have any ethical concerns regarding my participation in this study, I may contact the Protocol Officer for Ethics in Research, University of Ottawa, 550 Cumberland Street, Room 159, Ottawa, ON K1N 6N5 (613) 562-5841 or ethics@uottawa.ca.

There are two copies of the consent form, one of which is mine to keep.

Participant's signature: ______________________________ Date: ____________
(Signature) *(Date)*

Researcher's signature: ______________________________ Date: ____________
(Signature) *(Date)*

Appendix I

Calculation for drinking solutions

Group 1:

Glucose 300 mg/kg

(Weight in kg x 300)/198=amount of ml to administer (approx. 90 ml for someone who weighs 60 kg)

Group 2:

Glucose 650 mg/kg

(Weight in kg x 650)/198=amount of ml to administer (approx. 195 ml for someone who weighs 60 kg)

Group 3:

Glucose 1000 mg/kg

(Weight in kg x 1000)/198=amount of ml to administer (approx. 300 ml for someone who weighs 60 kg)

Group assignment: 1 2 3 (Circle)

Participant's weight: __________kg

Calculation:

Appendix J

Test instructions

Introductory instructions (adapted from the WAIS-III):

"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?"

CVLT-II Immediate Recall

Standard instructions for the immediate free recall of the list of words.

Instructions for the concomitant task:

"While listening to the list of words, I want you to do two motor sequences with both hands. The first sequence is: demonstrate the sequence (fist-chop-slap). The second sequence is: demonstrate the sequence (back-slap-chop-fist). Let's practice."

"You will do one sequence between each word on the list that I will read to you. After five words, you will have to change to the second sequence until another five words have been presented, after which you will switch back to the first sequence, and so on. You should keep track of the number of words that are read because you will not be told when to change sequences. Try to remember as many words as you can while performing the hand-movement task. You should share your attention equally between both tasks. Any questions?"

"Are you ready?"

Standard administration for the immediate recall of the interference list and the short-delay free and cued recalls.

Spatial Span

Standard administration

Grooved Pegboard Test

Standard instructions for the Grooved Pegboard Test

Instructions for the concomitant task:

"At the same time, I want you to put these screws in this block using your other hand. When I say go, begin here: (top right hole for left hand, or top left hole for right hand) and put the screws in the holes as fast as you can, using only your ____ (right, left) hand. Fill each row completely, from this side to this side (indicate which way) before moving on to the next row. You should share your attention equally between both tasks. Any questions?"

"Ready, go."

CVLT-II – Delayed Recall

Standard administration

Modified Brown Peterson Task (MBPT)

Description:

In the MBPT task, subjects are given orally series of 3 consonants at a fairly rapid rate (1 item per second). The screen must be turned away from the subject. The experimenter reads the consonants from the screen as they appear. The participant must remember these consonants after intervals of 9 and 36 seconds. During these intervals, the participant is required to count backwards out loud by threes from a number given by the experimenter. The participant is not allowed to repeat the consonants aloud at any time. After the presentation of the third consonant, the number is given and the participant has to count backwards until a tone is heard. This interpolated task typically hinders recall. Two delays will be used: 9 seconds and 36 seconds. The participant can start writing down the consonants after the tone. At the end of each series, subjects write the consonants they heard on a lined sheet of paper. Each series begins with 4 practice trials and continues with 10 experimental trials.

Instructions:

"I'm going to pronounce three consonant letters one at a time. When I am finished, I will give you a 3-digit number and ask you to count backward by 3. For example, if I gave you 133, then you would say… You would keep counting backward until your hear a tone. When you hear the tone, you stop counting. When you hear the tone, you try to write down the letters in exactly the same order as you heard them. I will now give you the recall sheet you will use. If you forget a letter, just leave a blank in the space where it should go on your recall sheet. Make sure you wait for the tone before writing down the letters. The first four will be practice. Are you ready to begin?"

Logical Memory I – Immediate Recall (WMS-III)

Modified instructions:

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

Record Time

Arithmetic (WAIS-III)

Standard administration

Alternate form:

Test Item	Correct Answer
5. $6.00, $3.00	$9.00
6. $7.00, $10.00	$3.00
7. 6, 24	4
8. 25 cents, 8	$2.00
9. 21, 3	7
10. 8, 20, $5.00	$3.40
11. 18, $9.50	$8.50

12. 9, $1.60, 20	20 cents
13. 2, $41.00, 1	$246.00
14. 15, 5, & 10	10
15. 1/3, 400	$1200.00
16. 315, 5	63 mph
17. $80.00, 15%	$68.00
18. $89.00	$44.50
19. 7, 8, 5	1 of 4 or 5 of 20
20. 9, 6 days	108

Stroop Colour and Word Test

Standard administration

Digit Span (WAIS-III)

Standard administration

Letter-Number Sequencing (WAIS-III)

Standard Administration

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

Modified instructions for delayed 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.

Standard administration for recognition

Appendix K

Motor concomitant task