Glucose Enhances Long-Term Declarative Memory
in Mildly Head-Injured Varsity Rugby Players

by

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We accept this thesis as conforming
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ABSTRACT

Cognitive deficits resulting from head injury have been likened to those experienced by elderly and Alzheimer's patients, especially with respect to declarative memory. Recent findings indicate that oral administration of glucose enhances memory, particularly in individuals with memory deficits (*e.g.* in the elderly and in people with Alzheimer's disease). Glucose enhancement of memory appears to be related to, and can perhaps be predicted by, an individual's ability to regulate glucose levels in their blood. The present investigation examined the degree to which cognitive deficits persist after mild head injuries (concussion) and if these deficits can be alleviated by glucose. Further, this study examined the relationship between blood-glucose regulation, mild head injuries, and the ability of glucose to enhance cognitive functions. Varsity rugby players, both with and without a history of head injury, were given glucose- or saccharin-sweetened beverages and then tested on a series of neuropsychological tests and had their blood-glucose levels monitored. Beverages and tests were administered in a counter-balanced, crossover design, enabling within-subject comparisons. Head-injured individuals were found to perform slightly worse than individuals with no history of head injury (controls) on the preliminary screening interview tests and tests of memory and divided attention given in the saccharin condition. In head-injured individuals, glucose enhanced performance on tests of long-term declarative memory and complex reaction time. In controls, glucose impaired performance on tests of long-term declarative memory but enhanced accuracy on a test of two-choice reaction time. The effects of glucose on memory appeared to be related to the subjects' glucose tolerance (ability to clear glucose from the blood).

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Dedication

I would like to dedicate this to my husband, Kevin, and my family, in thanks for their continuous support and encouragement.

Head injuries and resulting cognitive impairments represent a significant problem in today's society. Head injuries occur in about 3.6% of the population each year (Caveness, 1979), caused by motor vehicle accidents, falls, assaults, industrial accidents, and sports injuries. While mild head injuries are not life-threatening, there is evidence that they contribute to lasting cognitive impairments which can substantially impact work or academic abilities.

Deficits in attention are commonly reported following a head injury of any severity (Gronwall, 1991), with some types of attention being more susceptible to lasting impairment. One type of attention that may be compromised long after the occurrence of a head injury is information processing speed. Head injured patients are often unable to process information at a normal rate, as assessed by the paced auditory serial addition test (PASAT) (Gronwall, 1989; 1991; Gronwall & Wrightson, 1974; 1975) or tests of reaction time (MacFlynn, Montgomery, Fenton & Rutherford, 1984; Ponsford & Kinsella, 1992). Although the rate of information processing tends to return to normal within 35 days of the injury, Gronwall and Wrightson (1974) demonstrated that in some patients, the deficit may endure. A second type of attention that may be persistently affected is divided attention. This type of attention deficit may be evidenced when an individual has trouble performing more than one kind of activity simultaneously and especially under time pressure. Patients who had apparently recovered from closed head injury were shown to exhibit residual mental deficits on tests of divided attention, such as the consonant trigrams test (Gentilini et al., 1985; Stuss et al., 1985; Stuss, Stetham, Hugenholtz & Richard, 1989). A third type of attention deficit that may persist following head injury involves working memory. This type of attention is involved in processing information related to a stimulus after it has been removed from perception (Damasio & Anderson, 1993). Working memory may be abnormal for several weeks post-injury in some patients (Baddeley, Harris, Sunderland, Watts & Wilson, 1987; Newcombe, Rabbitt & Briggs, 1994), although this type of attention is not reliably found to be impaired from mild head injuries (Gentilini et al., 1985; Gentilini, Nichelli & Schoenhuber, 1989).

Deficits in memory represent another type of cognitive problem that may persist long after the occurrence of head injury. Levin and colleagues (1988) found that 28% of 42 patients tested 16 to 42 months following closed head injury had deficits in memory functioning. In general, immediate memory span has been found to be relatively resistant to the effects of head trauma and tends to improve more rapidly than long-term memory (Levin & Goldstein, 1989; Lezak, 1979). Long term memory for verbal information, or declarative memory, may be particularly affected, as evidenced by an abnormally rapid rate of forgetting in head-injured individuals (Levin, Benton & Grossman, 1982; Levin & Goldstein, 1989; Stuss et al., 1985). Declarative memory problems may be associated with even mild head injuries: Patients with post-concussion syndrome resulting from mild head injury showed impaired performance on declarative memory tests (Mariadas, Rao, Gangadhar and Hegde,1989).

Interestingly, head injuries have been likened to the aging process and Alzheimer's disease. Not only do these conditions have many similar neuropathological characteristics, including similar topographical distribution of lesions in the temporal region and presence of neurofibrillary tangles and neuritic plaques (Cope, 1986), but the psychological characteristics are also comparable. Substantial research evidence indicates that with age, humans experience a decline in the ability to learn and retain new information (Hock, 1987). Pharmaceutical approaches that augment cognitive deficits resulting from Alzheimer's disease or the aging process may also alleviate these problems in the head-injured.

Although results are somewhat equivocal, cognitive enhancing drugs, such as the nootropics, may improve cognition in geriatric and Alzheimer's patients (Hock, 1987). Recent findings suggest that one such nootropic, pramiracetam, also significantly improves memory (as measured by performance on a delayed recall task) in people who have sustained head injuries (McLean, Cardenas, Burgess & Gamzu, 1991). These drugs facilitate learning and retrieval of information (Nicholson, 1990; Wenk, 1989) presumably by increasing the availability of glucose for uptake and utilization in the brain (Wenk, 1989).

Recent investigations indicate that glucose, alone, may enhance cognition in individuals with memory problems. Indeed, researchers have consistently found that glucose administration enhances performance on memory tasks in humans (Craft, Zallen & Baker, 1992; Hall et al., 1989; Manning, Hall & Gold, 1990; Manning, Parsons & Gold, 1992; Manning, Ragozzino & Gold, 1993; Parsons & Gold, 1992), replicating effects found in lab animals (Gold, Vogt & Hall, 1986; Hall & Gold, 1986; Stone, Rudd & Gold, 1990). Although there have been a few reports of enhanced performance of young, healthy individuals on cognitive tasks following ingestion of glucose (Benton, 1990; Benton, Owens & Parker, 1994; Craft, Murphy & Wemstrom, 1994; Hall et al., 1989) glucose effects are especially apparent in individuals with pre-existing memory impairments, such as elderly individuals with age-related memory problems (Hall et al., 1989; Manning et al., 1990; Manning et al., 1992; Parsons & Gold, 1992) and patients with senile dementia of the Alzheimer's type (Craft et al., 1992; Manning et al., 1993). It is not yet known if memory in head-injured individuals would also be improved by glucose, but may depend on individual blood-glucose regulation (i.e. how quickly the blood-glucose level returns to baseline following glucose ingestion). Elderly individuals with memory impairments and Alzheimer's patients tend to have abnormal blood glucose regulation and possible impaired brain glucose utilization (Craft, Zallen & Baker, 1992; Gold & Stone, 1988). Following ingestion of glucose, the large increase in blood-glucose levels might attenuate such an impairment in brain-glucose utilization (Hall et al., 1989) and concomitantly enhance memory. In young, healthy adults, brain glucose is presumably already at an optimal level for memory processes. As a result, blood-glucose levels would not be expected to increase the brain's utilization of glucose and thus enhance memory further.

Although the mechanisms underlying the memory-improving action of glucose are not entirely known, there is growing evidence to suggest that circulating glucose levels might influence acetylcholine (Gold, 1991; Messier, Durkin, Mrabet & Destrade, 1990), a neurotransmitter believed to play a major role in memory (Bartus, Dean III, Beer & Lippa, 1982; Davis & Yamamura, 1978; Drachman & Leavitt, 1974; McGuire, 1990), and possibly attention (Warburton & Wesnes, 1984). This action may be mediated via an increase in the availability of acetyl coenzyme A (Gold, 1991; Kopf & Baratti, 1994; Messier et al., 1990; 1991), one of the precursors of acetylcholine. Recent evidence suggests that glucose facilitates acetylcholine synthesis particularly in the hippocampus (Messier et al., 1991), a brain structure strongly implicated in the storage and retrieval of new memories (Squire & Zola-Morgan, 1991) and frequently damaged in brain-injured individuals (Gurdjian & Gurdjian, 1976).

There has been some speculation as to which underlying memory process is particularly modulated by glucose. Manning, Parsons and Gold (1992) postulate that glucose ingestion enhances memory storage by preventing future degradation of memory. These researchers demonstrated that although immediate scores were similar in both the glucose and saccharin conditions, 24 hour recall of that same material was significantly greater when glucose had been ingested. This effect was apparent regardless of the relative time of administration (pre- vs. post- acquisition), suggesting that glucose influences storage of, rather than acquistion of, information. Retrieval processes may also be enhanced by glucose: In mice, glucose was shown to enhance learned performance when administered shortly before testing (Stone, Rudd & Gold, 1990). It is conceivable that glucose may exert its effects by influencing more than one type of cognitive process.

Performance on tasks requiring memory, particularly declarative memory, is especially improved. Ingestion of a glucose-sweetened beverage prior to testing improved retention on the Logical Memory subtest of the Weschler Memory Scale, or a similar type of narrative passage in elderly individuals (Craft et al., 1994; Hall et al., 1989; Gonder-Frederick et al., 1987; Manning et al., 1990; Manning et al., 1992; Parsons & Gold, 1992) and Alzheimer's patients (Craft et al., 1992; Manning et al., 1993). This finding has been expanded to include improved performance following glucose ingestion on another test of declarative memory: the Selective Reminding Task (Manning, Hall & Gold, 1990).

Although much of the research suggests that the cognitive-enhancing effects of glucose are limited to tests of long-term declarative memory, there is some evidence that attention and other nonmemory measures may be improved following ingestion of glucose. Benton (1990) found that normal young adults, who were given a drink containing glucose, showed a significantly greater rate of improvement than controls on a task of selective attention. In addition, Benton, Owens & Parker (1994) showed that in young adults, glucose not only improved reaction times on the Rapid Information Processing Task, but also selectively enhanced scores on the most cognitively demanding subtest of the Stroop Task. These researchers believe that glucose likely has a general effect on cognition rather than a specific influence on the consolidation of memory. Conversely, Allen and colleagues (1996), who demonstrated enhanced performance of elderly individuals on nonmemory tasks (verbal and figural fluency), conclude that glucose may have facilitated the retrieval mechanisms involved in these tasks.

The present investigation examined the possibility that glucose administration might improve memory and attention deficits in individuals with mild head injuries. As previously mentioned, cognitive sequelae resulting from head injuries have been likened those resulting from the aging process and Alzheimer's disease. These deficits, particularly those in declarative memory, appear to be amenable to glucose enhancement in elderly and Alzheimer's patients. However, the ability of glucose to enhance memory may depend on blood-glucose regulation, which is frequently impaired in elderly and Alzheimer's patients. The present investigation sought to determine whether glucose enhancement of cognition can be extended to include individuals with attention and memory deficits resulting from mild head injury. A second aim of this study was to investigate the relationship between these cognitive deficits and blood glucose tolerance in these individuals.

Varsity rugby players, both with, and without a history of head injury, and resulting cognitive deficits, served as subjects in this experiment. It was previously mentioned that even individuals with mild head injuries may suffer lasting cognitive impairment that could affect work or academic abilities. University athletes represent a population that is particularly susceptible to mild head injuries and resulting cognitive impairments and, surprisingly, hasn't received much attention in the literature. There is reason to believe that a substantial proportion of university students, particularly those involved in a contact sport, such as football (Alves, 1991; Alves, Rimel & Nelson, 1987; Barth et al., 1989; Reid, Tarkington, Epstein & O'Dea, 1971; Willberger, 1993) or rugby (Gronwall, 1992; Ingersoll, 1993; Sparks, 1985; Wrightson, 1992), have received one or more head injuries. A retrospective study indicated that 24% of male students in the general college poplulation had reported a previous head injury with loss of consciousness (Crovitz, Horn & Daniel, 1983). This incidence rises to 42% in varsity football players, in which many individuals report associated attention and memory impairments (Barth et al., 1989). Repeated mild head injuries, which may affect as many as 22% of varsity football players (Barth et al., 1989) and a similar large proportion of rugby players (Wrightson, 1991), likely have a cumulative effect on cognitive functioning. For example, Gronwall and Wrightson (1975) demonstrated that information processing speed was significantly reduced and took longer to recover in individuals who had sustained two concussions compared to individuals who had sustained only one concussion. This finding implies that mild head injuries, and particularly repeated concussions, may detrimentally affect a varsity athlete's ability to perform well on cognitive tasks and academic studies. Due to the nature of rugby (i.e. it is a contact sport with the potential for injury and helmets are not worn), we expected that rugby players may be particularly affected by head injuries and associated cognitive problems. It is for these reasons, as well as availability, that we chose to study varsity rugby players in the present investigation.

The ability of glucose to enhance cognition may be particularly relevant in individuals with mild head injuries, such as varsity rugby players, as their cognitive deficits are relatively subtle. Presumably, an optimal dose of glucose may be able to enhance cognitive performance in this population to, or near to, the level of controls. As glucose is known to enhance cognitive performance in an inverted-U dose response manner (Parsons & Gold, 1992), it was important that the optimal blood-glucose level was obtained during testing. Previous studies reported hyperglycemic enhancement of cognition in elderly individuals at blood-glucose levels between 150 mg/dL and 175 mg/dL (Parsons & Gold, 1992), which are are generally considered to be normal post-meal levels. Glucose doses of 50 g (Craft, Murphy & Westrom, 1994; Hall et al., 1989) via oral ingestion have been shown to increase mean blood-glucose levels from baseline (early morning measurements after overnight abstinence from food) of 90-115 mg/dL to this optimal level.

The types of cognitive functions tested in this study were those that were expected to be most susceptible to impairment following mild head injury, as well as subsequent enhancement by glucose. These cognitive functions include: declarative memory, information processing speed, divided attention, and working memory. In addition, we tested passive memory for nonverbal information. Declarative memory, both contextual and noncontextual, was assessed with the Logical Memory subtest (with immediate and 24 hour delayed recall) from the Wechsler Memory Scale-Revised (WMS-R) and a paired associates task (with immediate and 24 hour delayed recall), respectively. Both of these tasks have been shown to be sensitive to assessing subtle deficits in declarative memory in head-injured patients (Stuss et al., 1985), and, as previously mentioned, the Logical Memory test, particularly with delayed recall, is also sensitive to glucose enhancement. Information processing speed was assessed using the Symbol Digits Modalities Test (SDMT), and three measures from a computerized test battery (simple reaction time test, complex reaction time test, and the Running Memory CPT). The SDMT has been reported to be a good measure of overall information processing ability (Cohen, 1993; Ponsford & Kinsella, 1992), it is sensitive to head injury (Lezak, 1983; Ponsford & Kinsella, 1992) and it is relatively resistant to practise effects (Feinstein, Brown & Ron, 1994). Simple and complex reaction time tests have also been reported to be good measures of information processing speed, and are sensitive to deficits associated with head injury (Braun, Daigneault & Champagne, 1989; MacFlynn et al., 1984; Ponsford & Kinsella, 1992; Stuss et al, 1989b; Van Zomeran & Deelman, 1978). The Running Memory CPT closely resembles the PASAT, a test that is reported to be one of the best measures of information processing speed (Ponsford & Kinsella, 1992), with the exception that there is no arithmetic involved. Divided attention (and memory for information under conditions of interference) was assessed using the Brown-Peterson Consonant Trigrams Task (CCC). Stuss and colleagues (Stuss et al., 1985; Stuss, Stetham, Hugenholtz & Richard, 1989) demonstrated that this test is sufficiently sensitive to differentiate mildly head-injured patients (who had experienced good recovery) from their matched controls. Working memory was assessed by administering a test of listening span during the screening interview, and the Tower of Hanoi puzzle from a computerized test battery for the experimental part of the study. While listening span is considered to be a good measure of verbal working memory capacity (Daneman & Carpenter, 1980), the Tower of Hanoi is considered to be a good measure of nonverbal working memory ability (Damasio & Anderson, 1993). In addition, we assessed passive memory for nonverbal material by administering the SDMT with incidental recall.

Each subject (head-injured and control groups) ingested a beverage sweetened with glucose or saccharin prior to being tested on the series of neuropsychological tests. The following day, the other sweetener was given and the subjects were tested on matched neuropsychological tests. By having each subject experience both conditions, we could determine the effects of glucose (relative to saccharin) on cognition for each individual. To examine the relationship between head injuries and blood-glucose regulation, blood-glucose levels were monitored for the duration of both testing sessions.

It was expected that individuals with a history of head injury would not perform as well as controls on the neuropsychological tasks, at least in the saccharin (placebo) condition. However, we expected that glucose would enhance the performance of head-injured students, particularly on delayed recall for a declarative memory task. Control subjects were not expected to exhibit enhanced performance on these tasks following glucose ingestion. In addition, we speculated that cognitive impairments might be accompanied by deficits in blood-glucose regulation.

Methods

Subjects.

The participants were 24 male undergraduate students from the University of Victoria, who were members of one of the four school rugby teams ($\underline{n}$ = 20), or were involved in a similar team sport ($\underline{n}$ = 4). Subjects received either financial compensation ($10) or bonus points toward the Introductory Psychology course upon completion of their participation. The subjects ranged in age from 18 to 24 years (control group : $\underline{M}$ = 19.6; head-injured group: $\underline{M}$ = 19.9) and had between 14 and 17 years of education (control group: $\underline{M}$ = 14.6; head-injured group: $\underline{M}$ = 15.3). During a preliminary screening interview, information regarding health (see Appendices A & B) was collected from each individual and it was determined that all subjects were nondiabetic and in good health. In addition, subjects were questioned about their injury history (Appendix C) and cognitive functioning was assessed by their performance on two tests: information processing speed and passive memory for nonverbal information were assessed with the Symbol Digit Modalities Test (SDMT)(Smith, 1968; 1973) with incidental recall, and working memory capacity was assessed with the Listening Span Test (Salthouse & Babcock, 1991) (see Appendix D). The results from the injury history reports and the cognitive tests indicated that 12 subjects had no history of head trauma (control group), while the other 12 subjects had received one or more concussions within the past ten years (mildly head-injured group).

Procedure.

The testing regimen used in this study was adapted from Hall & colleagues (1989): A repeated measures counterbalanced crossover design was employed in which each subject was tested under two different sweeteners (glucose and saccharin) and two equivalent sets of neuropsychological tests. Subjects were individually tested and were blind to sweetener condition.

The subjects participated in three consecutive morning sessions at the same time each day, between 7:30 am and 11:30 am. All subjects were instructed to come to the testing room each morning having fasted from midnight the night before. Upon arrival at the first session, subjects were told that the purpose of the experiment was to evaluate the effects of artificial versus natural sweeteners on attention and memory and were briefly introduced to the experimental methods. An informed consent form outlining the purpose and methods was then given to subjects to sign, if they wished to continue participation in the study (see Appendix E).

Baseline blood-glucose levels were measured using a Glucoscan One Touch Basic meter (Lifescan, Inc.) at the commencement of all three testing sessions. Blood samples were taken again 15 and 50 minutes after beverage ingestion for the first and second testing sessions to assess glucose levels and clearance rates. This procedure, which is virtually painless, involved pricking the subject's finger with a penlet and placing one drop of blood on an enzyme pad which was then read by a reflectance meter. The experimenter wore latex gloves for this procedure and disposed of lancets and test strips in a special biohazard waste container. Lancets were changed each time and the collection site was swabbed with alcohol before each sample was taken.

After initial measurement of baseline blood-glucose levels, the subjects ingested a 16 ounce lemon-lime flavoured beverage sweetened with either saccharin (47.4 mg) or glucose (50 g, with 23.7 mg saccharin added to equate for taste). Beginning three minutes after drinking the beverage, the subjects were tested on the following series of neuropsychological tests:

Logical Memory (LMS).

This subtest of the Wechsler Memory Scale-Revised (Russell, 1975) was used to assess declarative memory. Prior to listening to a narrative passage containing 25 units of information (phrases), subjects were notified that they would be asked to recall the passage both immediately after presentation and 24 hours later. The following day, 24 hour recall was tested without repetition of the narrative passage. Recall was measured as the total number of correctly recalled units, each worth one point.

Paired Associates (PA).

This test was used to assess non-contextual declarative memory. Two equivalent sets of eight word pairs each (see Appendix F) were constructed from an original set of 30 word pairs (Jones 1974) using associative difficulty ratings provided by 25 university students. Prior to listening to a list of eight word pairs (5 of which were concrete and 3 of which were abstract), subjects were notified that they would be asked to recall the word pairs immediately after presentation and again 24 hours later. After the list was read out, the first word in each pair was presented and the subjects were asked to recall its associate. The following day, 24 hour recall was tested without repetition of the list. One point was given for each correct answer.

Auditory Consonant Trigrams (CCC).

This task (Brown, 1958; Peterson & Peterson, 1959), which tests recall of auditory information under conditions of interference, was used to assess divided attention. Upon hearing three consonants followed by a number, subjects were to immediately begin counting backward from that number by threes until instructed to stop (i.e. after a delay of 0, 9, 18, or 36 seconds). At this time, the subjects were asked to recall the three consonants. Five trials at each of four time delays were administered. One point was given for each correctly recalled letter.

Symbol Digit Modalities Test (SDMT).

This test, developed by Smith (1968, 1973), was used to assess information processing speed. The subjects were given a "key" with nine symbols, each corresponding to a number from one to nine. During a 90 second trial, the subject was to write in the correct number that corresponded to each given symbol, working quickly and accurately to correctly complete as many of the 110 items as possible. One point was given for each correct answer.

SDMT Incidental Recall (SDMT-D).

This test was used to assess passive memory for nonverbal material. Following a five minute filled delay, in which the Logical Memory subtest was administered, subjects were asked to complete 15 items from memory.

ANAM Battery.

The following four tests, which are part of the Automated Neuropsychological Assessment Metrics (ANAM) battery (Reeves, Thorne, Winter & Hegge, 1989; Kane & Kay, 1992) were administered via a 386 DX IBM compatible computer with a three-button mouse. Accuracy, response time and efficiency (a composite measure of accuracy and speed) were recorded.

Simple Reaction Time (SRT). This test measures the speed of reaction to a single stimulus and thereby assesses a low level of information processing. The subjects were to press the left button on the computer mouse as quickly as possible following the presentation of an asterisk on the computer screen. The test, which included a list of instructions, five practise trials and 25 test trials, took about one minute to complete.

Two-Choice Reaction Time (2-CH). This test measures speed of two different reactions to two different stimuli, thereby assessing a slightly higher level of information processing than simple reaction time. The computer randomly displayed one of two different symbols (an asterisk and or a cross). The subjects were to respond by quickly pressing the left button if the asterisk was shown and the right button if the cross was displayed. Instructions and five practise trials preceded the 45 test trials, with the entire test taking about three minutes to complete.

Running Memory Continuous Performance Test (RM-CPT). This test was used to assess information processing speed. The computer displayed a random series of letters (one at a time) to which the subject was to respond by pressing the left button if the letter being shown matched the one that came immediately before it, or the right button if the letter being shown was different from the previous letter. This test included a list of instructions, 10 practise trials and 160 test trials which took a total of about five minutes to complete.

Tower of Hanoi Test. This test was used to assess working memory. The computer displayed three posts, each of which had some blocks of varying sizes stacked on them. The object of the task was to place all of the blocks on the middle post, with the largest block on the bottom and successively smaller blocks stacked so that the smallest block was at the top of the stack. Blocks could be moved, one at a time, to another post (by pressing two number keys on the keyboard, corresponding to the number of the source and target posts), with the condition that larger blocks could not be placed on top of smaller blocks. The subjects were given a list of instructions, two practise tests and six test trials, each taking a maximum of two minutes.

The first session lasted about one hour. It began with determining baseline blood-glucose levels and then beverage administration. The neuropsychological tests were then administered in the following order: CCC, Paired Associates, Simple Reaction Time, Two-Choice Reaction Time, Running Memory CPT, SDMT, Logical Memory, SDMT Incidental Recall, Tower of Hanoi.

Long-term (24 hr) retention of items from the Logical Memory subtest and the Paired Associates test was assessed the following morning, at the start of the second session. The second testing day was identical to the first, except the other beverage condition (glucose or saccharin) was tested and equivalent versions of the same neuropsychological tests (except for the CCC, in which the same version was used on both testing days) were employed.

On the third testing day, long-term retention of items from the previous day's versions of Logical Memory and Paired Associates tasks was tested and the subjects were then debriefed and thanked for their participation in the study. Debriefing consisted of providing the subjects with additional information about the hypotheses and requesting that they not disclose this or the contents of the tests to other potential subjects (see Appendix G). Subjects were also asked to guess the identity of each drink (artificially versus naturally sweetened) and to comment on their perception of the cognitive and performance effects of each drink, and also about the presence of extenuating circumstances that might have affected their performance (e.g. amount of sleep the previous night).

Results

As the screening interview revealed, the mean number of head injuries ranged from zero to 14. Those with at least one head injury had a mean of 4.33 (standard deviation of 3.55) and a modal number of 2 head injuries. Interestingly, 11 of the 12 head-injured individuals had experienced at least two head injuries. Duration of loss of consciousness and post-traumatic amnesia were difficult to ascertain with accuracy, but seemed to range from no loss of consciousness to one minute, and from one minute to a few hours of post-traumatic amnesia. Comparison of the performance of head-injured subjects to controls on all tests for the screening interview and saccharin condition revealed selective and subtle deficits. The head-injured individuals scored slightly lower than controls on four measures: SDMT- Delayed Incidental Recall (SDMT-D), all measures of the Listening Span (LS-SPAN, LS-TRIALS, LS-ITEMS) (see Figures 1 & 2), the CCC and LMS-D (see Figures 3 & 4) (one-tailed t-tests, $p < .05$). However, head-injured individuals did not differ from controls with respect to performance on the SDMT, PA-I, PA-D, LMS-I, and all tests from the ANAM battery. There appeared to be a cumulative effect of concussions on memory, as the number of head injuries per individual was significantly correlated with performance on the LMS-D in the saccharin condition (Pearson $r = -.615$, $p < .033$).

Blood-glucose readings from head-injured and control groups for the glucose and saccharin conditions are compared in Figure 5. There were no significant differences between the control and head-injured groups on baseline blood-glucose levels for the

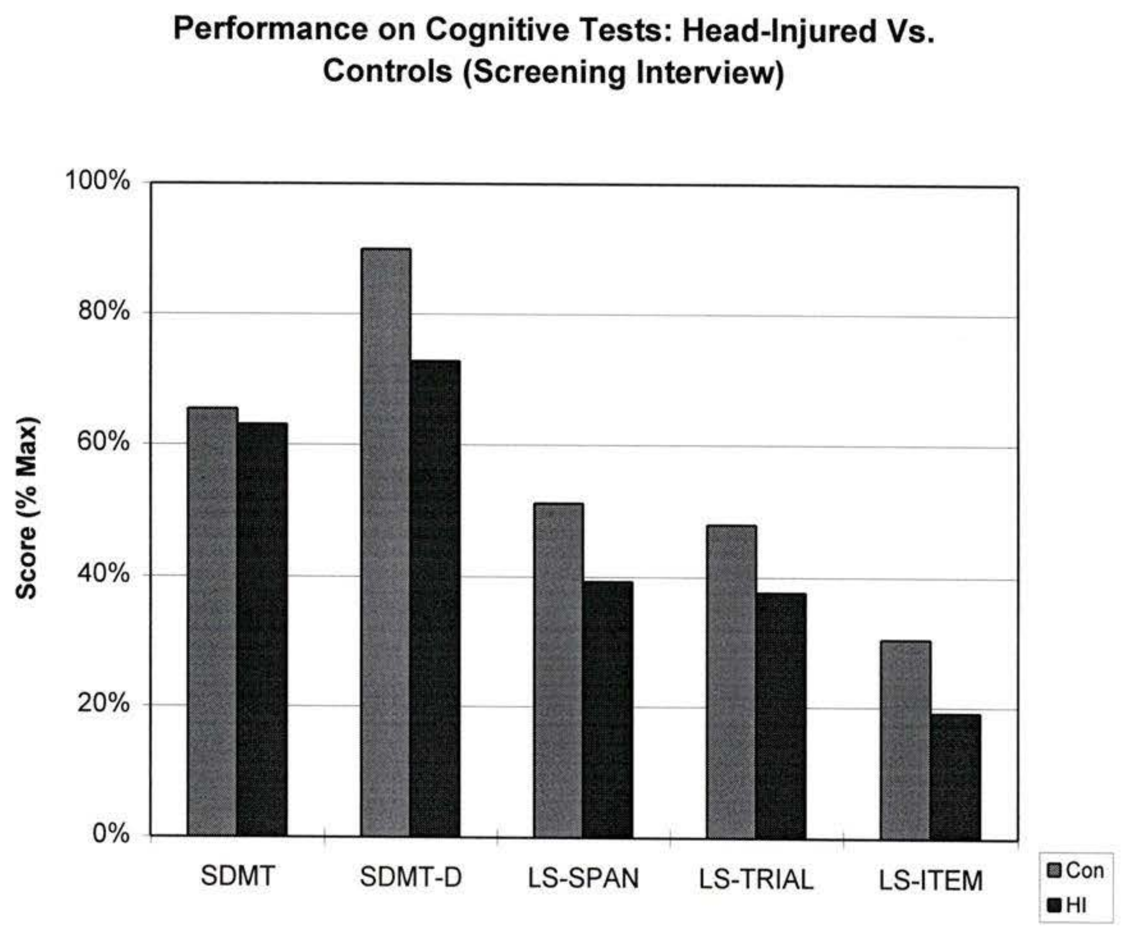

Figure 1. The differences between the head-injured and control groups for percent correct on screening interview tests (SDMT = Symbol Digit Modalities Test; SDMT-D = Symbol Digit Modalities Test with delayed incidental recall; LS = Listening Span).

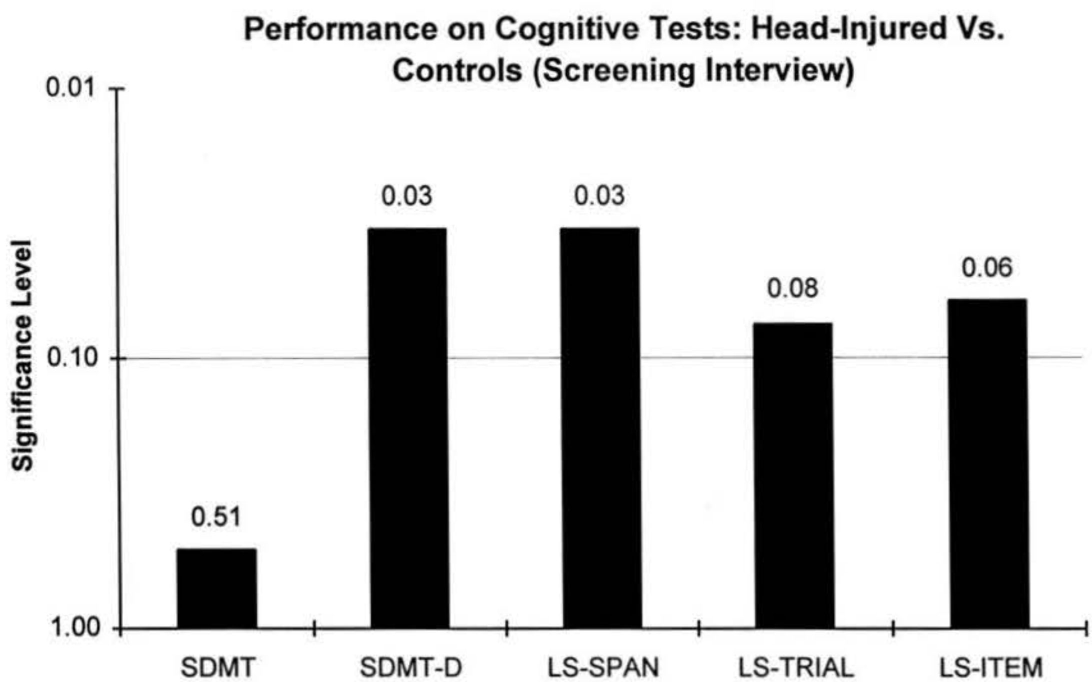

Figure 2. Significance levels of the differences in performance between the head-injured and control groups on screening interview tests (SDMT = Symbol Digit Modalities Test; SDMT-D = Symbol Digit Modalities Test with delayed incidental recall; LS = Listening Span).

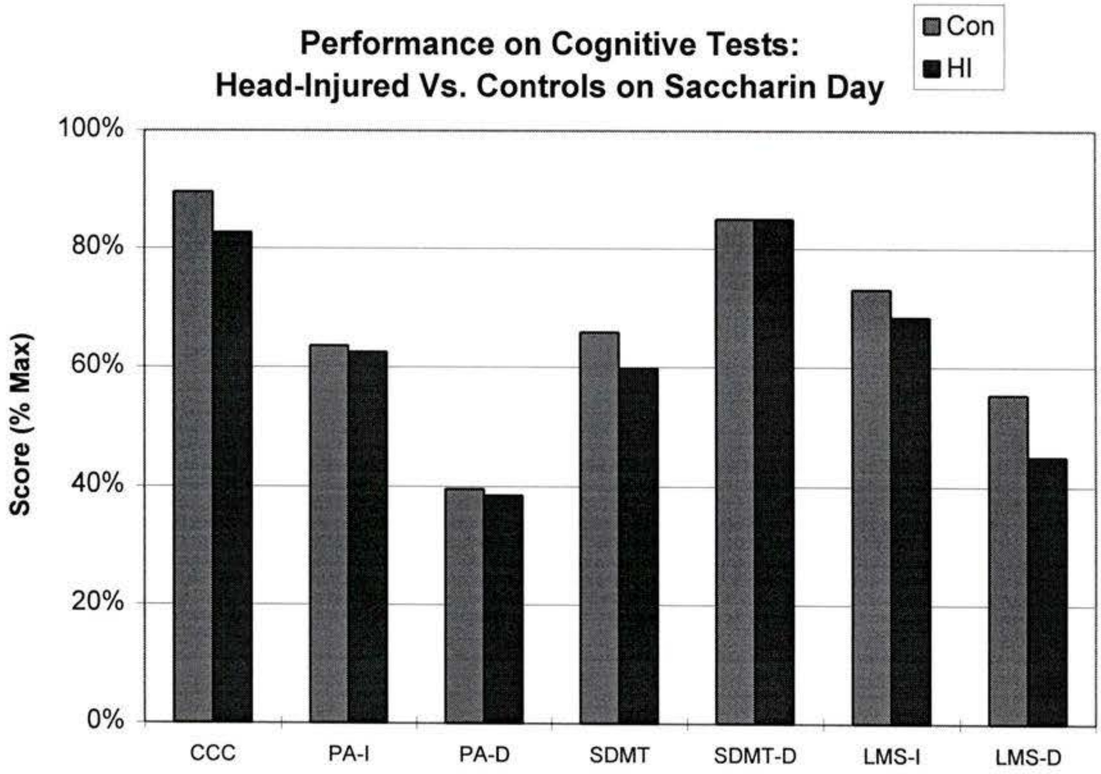

Figure 3. The differences between the head-injured and control groups for percent correct on tests given on the saccharin day (CCC = Consonant Trigrams Test; PA-I = Paired Associate task with immediate recall; PA-D = Paired Associate task with delayed recall; SDMT = Symbol Digit Modalities Test; SDMT-D = Symbol-Digit Modalities Test with delayed incidental recall; LMS-I = Logical Memory Scale with immediate recall; LMS-D = Logical Memory with delayed recall).

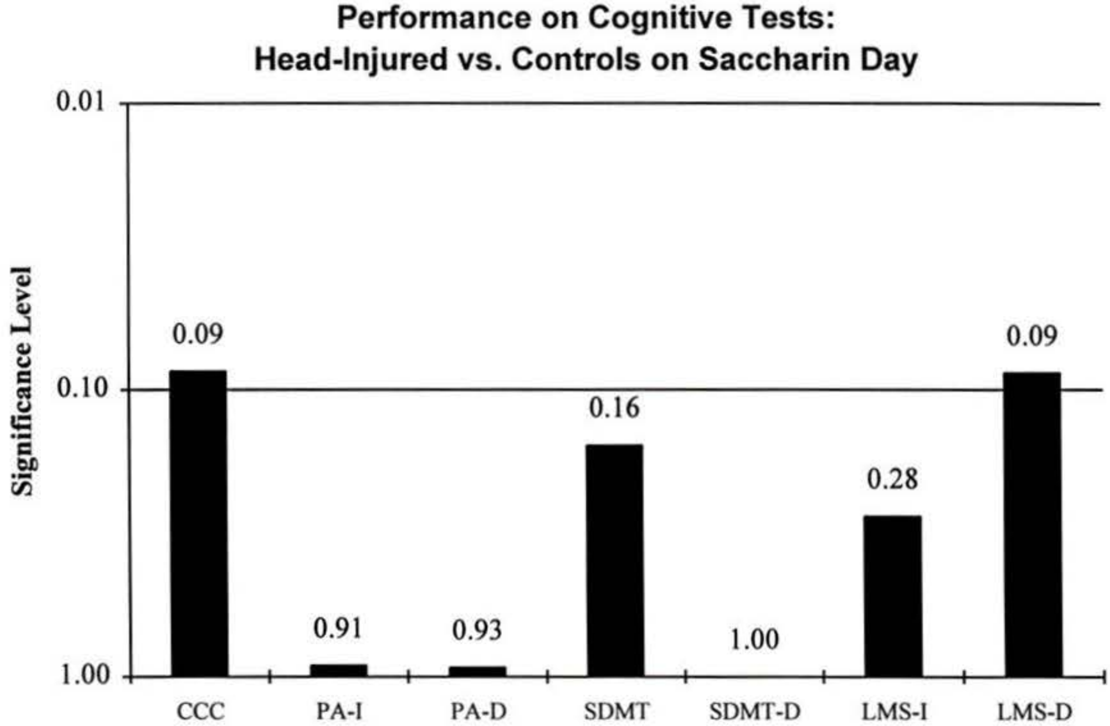

Figure 4. Significance levels of the differences in performance between the head-injured and control groups on tests given on the saccharin day (CCC = Consonant Trigrams Test; PA-I = Paired Associate task with immediate recall; PA-D = Paired Associate task with delayed recall; SDMT = Symbol Digit Modalities Test; SDMT-D = Symbol-Digit Modalities Test with delayed incidental recall; LMS-I = Logical Memory Scale with immediate recall; LMS-D = Logical Memory with delayed recall).

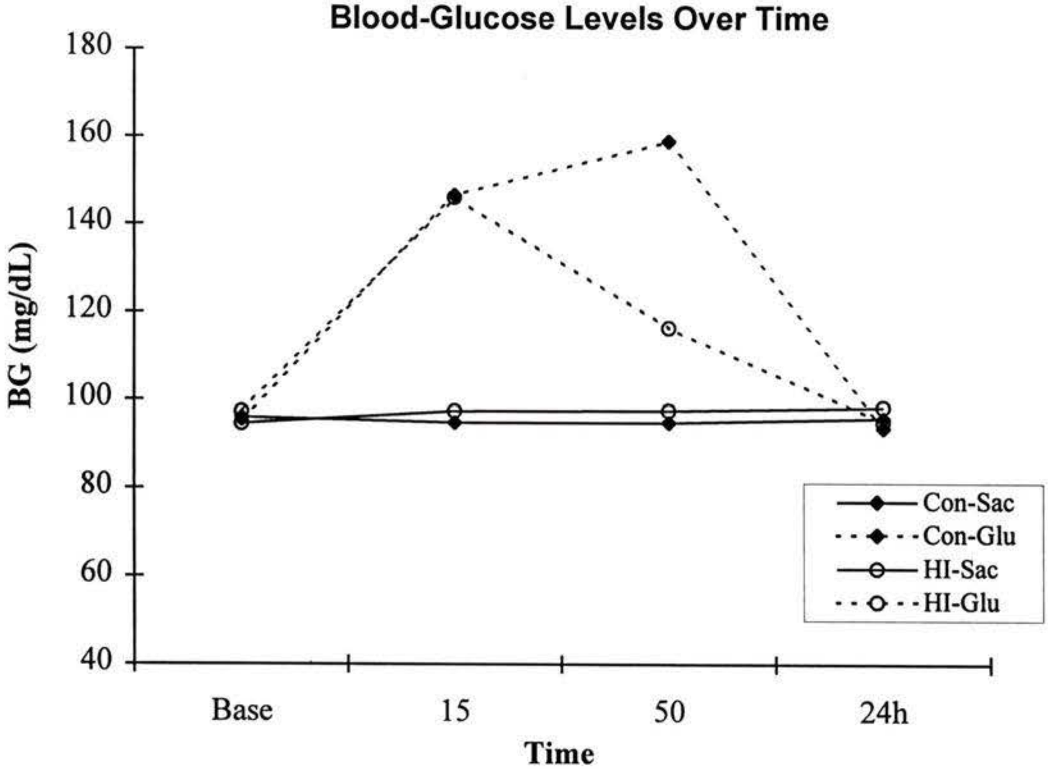

Figure 5. Group mean blood-glucose levels for each monitoring point throughout the testing sessions (Con = control; HI = head-injured; Sac = saccharin; Glu = glucose; BG = blood-glucose).

saccharin or the glucose day. While the saccharin beverage did not change blood-glucose levels from baseline in either of the two groups (all p's > .05), ingestion of 50 g glucose significantly elevated blood-glucose levels in both groups at 15 min post-ingestion (paired t-tests between baseline & 15 min levels, p's <.001). Peak blood-glucose change (maximum of 15 min or 50 min) was not significantly different between the two groups ($t(22) = 1.81$, $p < .08$, ns). However, at 50 min, blood-glucose was still high in the control group, but had dropped significantly in the head-injured group (paired t-test between 15 & 50 min levels within the head-injured group, $t(11) = 3.60$, $p < .004$) and was significantly lower than the level of the controls ($t(11) = 2.76$, $p < .01$).

Glucose significantly influenced long-term declarative memory, although in different ways in the head-injured and control groups: Glucose enhanced long-term declarative memory in the head-injured group, while it impaired long-term declarative memory in the control group, as shown by performance on the Logical Memory Scale measures. A comparison of the two groups (control, head-injured) on the difference in condition (saccharin and glucose conditions) for performance on the LMS-D revealed a significant interaction effect ($F(1,22) = 11.46$, $p < .003$). Relative to the saccharin day, the head-injured group scored significantly higher on the glucose day (paired $t(11) = -3.39$, $p < .007$), while the controls scored significantly lower (paired $t(11) = -2.29$, $p < .04$). As Figure 6 shows, glucose enhanced long-term declarative memory in the head-injured group almost to the level of the controls in the saccharin condition. To examine whether glucose's effect on memory was due to a change in retention,

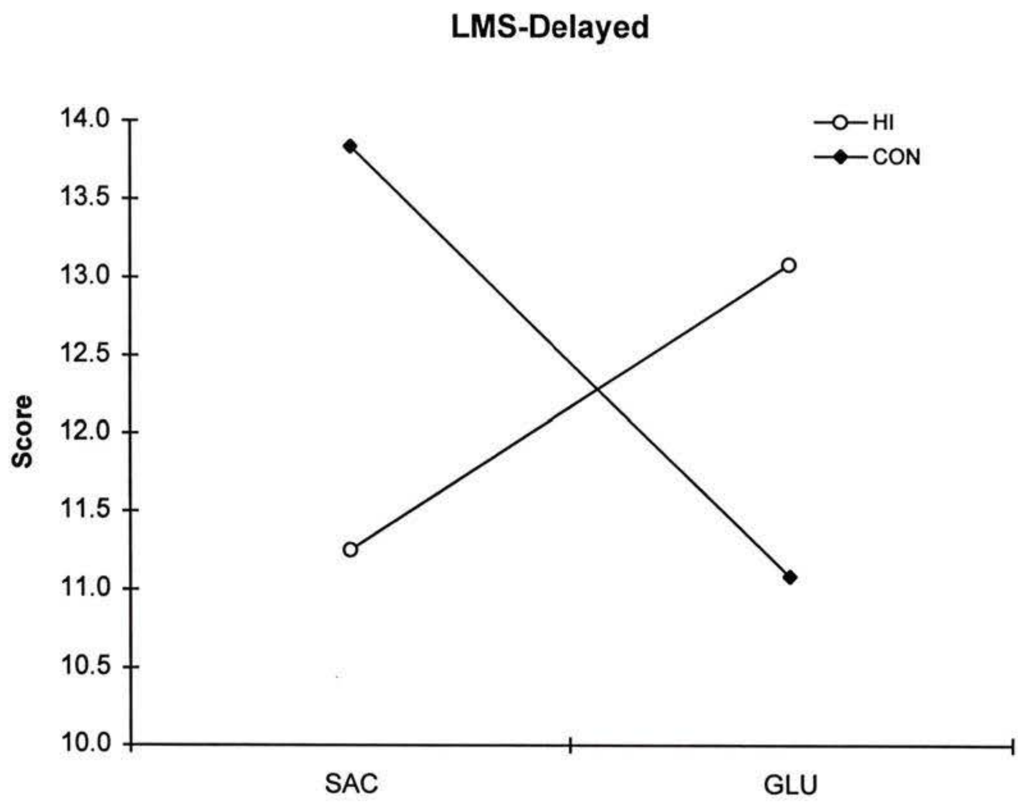

Figure 6. Performance on the Logical Memory Scale-Delayed (LMS-D) of head-injured (HI) and control (CON) subjects on glucose (GLU) and saccharin (SAC) days.

proportional savings scores were calculated to compare test performance immediately after learning to test performance 24 hours later [1 - (LMS-I - LMS-D)/LMS-I]. The higher the proportional savings score, the greater the amount of information retained. A repeated measures ANOVA comparing glucose and saccharin condition scores of the two groups on the LMS-SAV revealed a significant interaction, $F(1,22) = 7.84$, $p < .01$ (see Figure 7). The controls retained significantly less information from the glucose day than from the saccharin day (paired t-test on LMS-SAV within control group, $t(11) = 2.15$, $p < .05$). In contrast, the head-injured individuals tended to retain more information from the glucose day than from the saccharin day (paired one-tailed t-test within head-injured group, $t(11) = 3.04$, $p < .04$). In fact, on the day after glucose, the head-injured retained as much, if not more, than the controls (t-test on differences between controls and head-injured groups on LMS-SAV, glucose day, $t(22) = 1.96$, $p < .06$, ns).

Glucose enhanced accuracy of the controls and reaction time of the head-injured individuals on the complex 2-choice reaction time test (2-CH). As Figure 8 shows, glucose enhanced accuracy in the control group, while having no real effect on accuracy in the head-injured group. A repeated measures ANOVA on the glucose and saccharin condition scores for accuracy on the 2-CH revealed a significant interaction between group (control, head-injured) and sweetener, $F(1,22) = 8.07$, $p < .009$, and a paired t-test on 2-CH accuracy within the control group revealed that controls scored significantly higher on the glucose day relative to the saccharin day ($t(11) = 2.26$, $p < .045$). As Figure 9 shows, glucose significantly improved (decreased) reaction times on this same

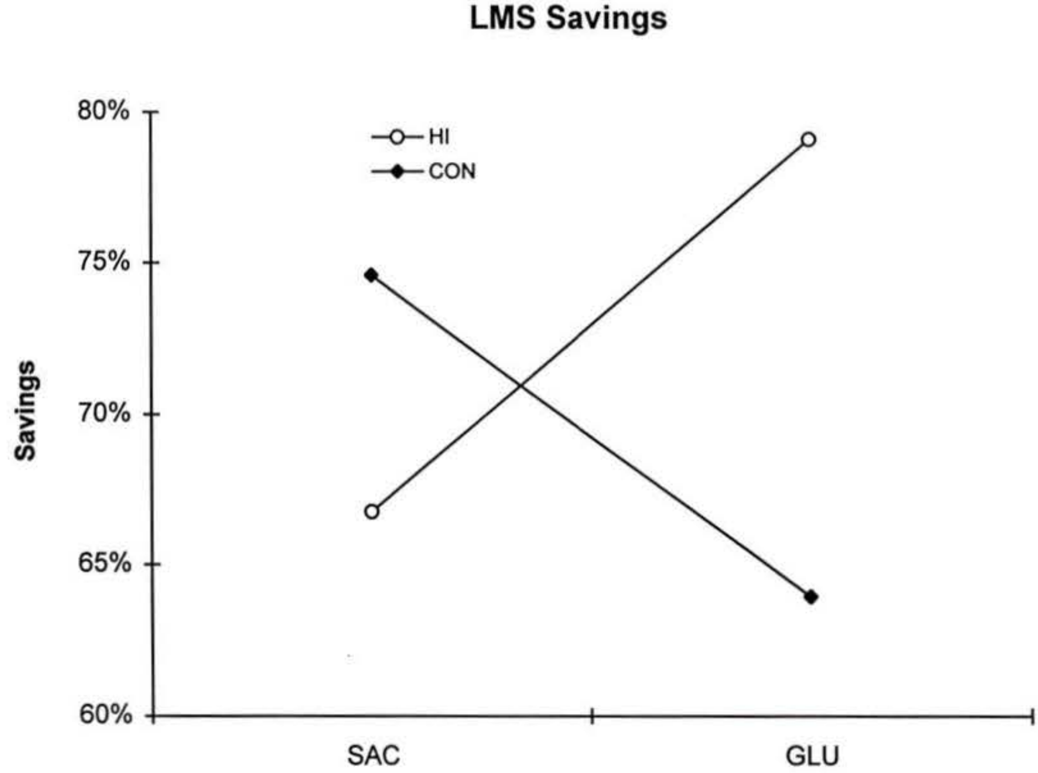

Figure 7. Savings on the Logical Memory Scale. Performance on the delayed test (LMS-D) as a percentage of performance on the immediate test (LMS-I) for head-injured (HI) and control (CON) subjects on glucose (GLU) and saccharin (SAC) days.

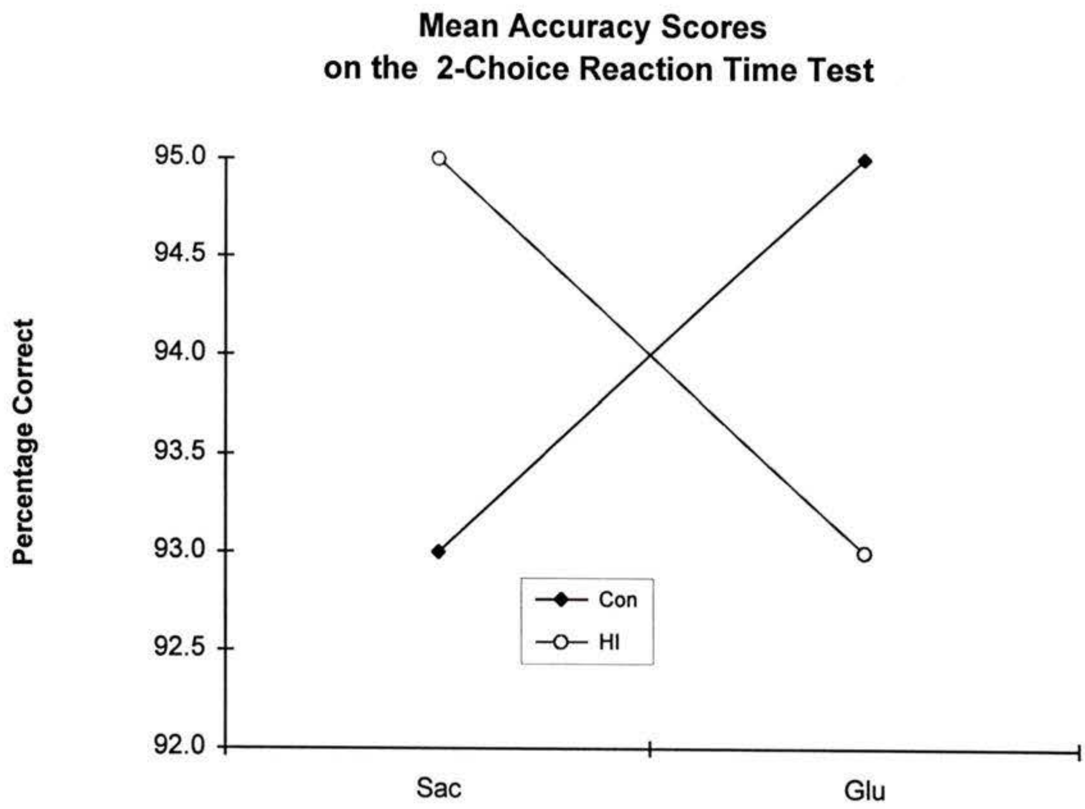

Figure 8. Mean accuracy scores of the head-injured (HI) and control (Con) groups on the 2-Choice Reaction Time test on glucose (Glu) and saccharin (Sac) days.

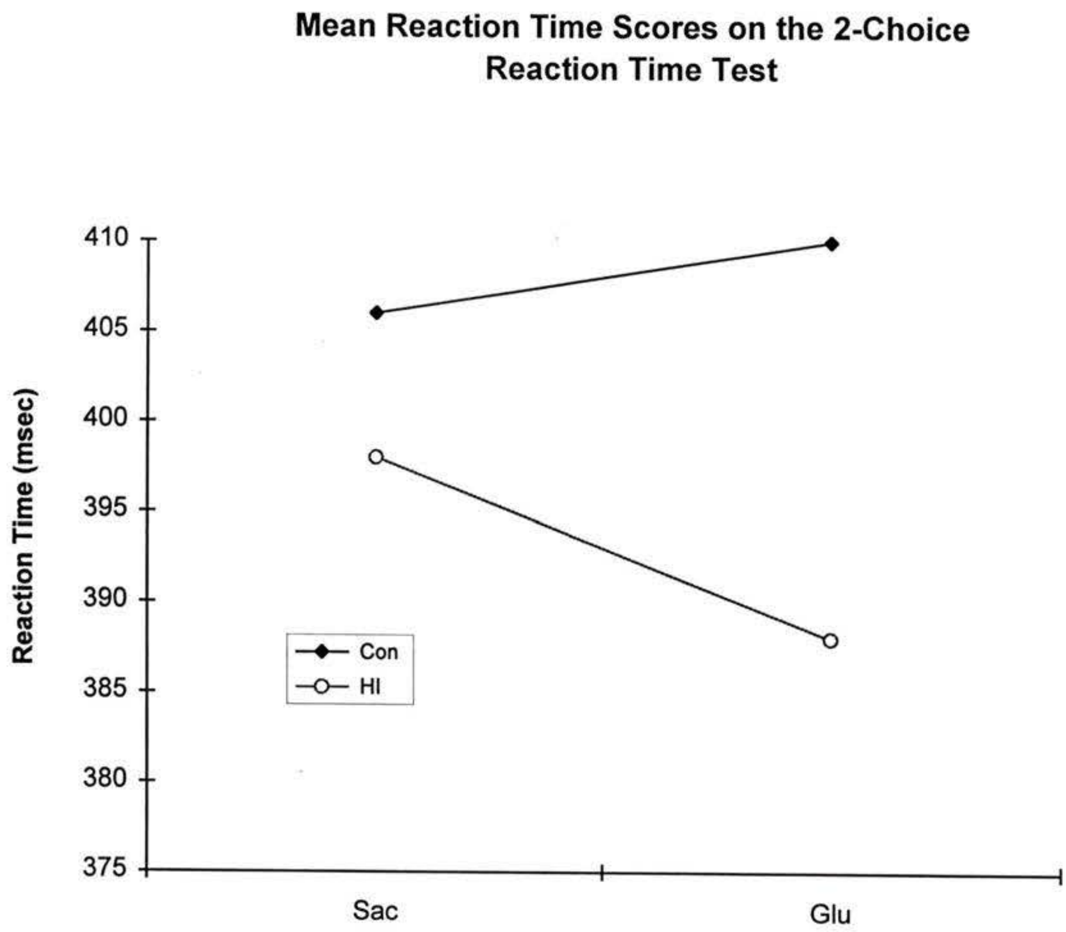

Figure 9. Mean reaction time scores of the head-injured (HI) and control (Con) groups on the 2-Choice Reaction Time test for both the glucose (Glu) and saccharin (Sac) days.

task in the head-injured group but not the control group (paired t-test on 2-CH reaction time within the head-injured group, $t(11) = -2.64$, $p < .023$). Efficiency scores (composite measure of accuracy and reaction time) were not affected by glucose. This suggests that glucose may have slightly compromised reaction time in the controls and accuracy in the head-injured individuals, though neither of these effects were significant.

There was no evidence that glucose affected information processing speed (3 measures), divided attention, passive memory for nonverbal information, working memory, short-term and long-term noncontextual declarative memory, and short-term contextual declarative memory, in that there were no significant differences between performances in the glucose and saccharin conditions for SDMT, RM-CPT, SRT, CCC, SDMT-D, Tower of Hanoi, PA (immediate & 24-hr recall), or the immediate recall of the LMS, respectively (all p's > .05). However, subtle glucose effects on divided attention and information processing speed may have been masked by significant practice effects on the CCC (paired t-test, $t(23) = -4.85$, $p < .001$), and differences between the two versions of the SDMT(paired t-test, $t(23) = -4.67$, $p < .001$), respectively.

Blood-glucose recovery (i.e. the change in blood-glucose readings from 15 min to 50 min post-ingestion of the glucose beverage), which tended to be quicker in the head-injured than the control group, was significantly correlated with glucose enhancement of memory. In particular, individuals with quicker blood-glucose recovery remembered more on the 24-hr recall of the Logical Memory Scale (LMS-D) when given glucose rather than saccharin: Blood-glucose recovery (15 - 50 min) was significantly correlated with difference scores (glucose - saccharin) for 24-hr recall of the LMS, $r = .55$, $p < .006$, as well as with difference scores on the LMS-SAV, $r = -.56$, $p < .005$.

The debriefing session revealed that prior knowledge of the research hypotheses would not have influenced performance, as subjects could not correctly identify which drink was sweetened with glucose. A chi-square analysis revealed that the number of correct guesses was not significantly different from chance, $\chi^2(1, N{=}24) = 0.17$, $p = .88$.

Discussion

In general, the present investigation found that subtle and specific residual deficits in cognition may result from mild head injuries. Glucose was shown to selectively alleviate deficits in long-term declarative memory and also improved complex reaction time in head-injured individuals. In individuals with no history of head injury (controls), glucose impaired long-term declarative memory but enhanced accuracy on a complex reaction time test. The effects of glucose on memory were related to a subject's ability to clear glucose from the blood.

Mild head injuries may produce residual cognitive deficits. In particular, head-injured individuals appeared to have subtle deficits in passive memory for nonverbal material, working memory, divided attention, and long-term declarative memory: Head-injured individuals scored slightly lower than controls on the SDMT-Incidental Recall, the Listening Span Test (both from the screening interview) and the CCC and LMS-D (for the saccharin condition).

Passive memory for nonverbal information appeared to be impaired, at least initially, in individuals with mild head injuries. This impairment was evident in the lower scores obtained by the head-injured individuals compared to controls on the SDMT-D for the screening interview but not subsequent administrations. Because subjects had been previously exposed to this test, it is likely that they anticipated re-testing, thereby changing the nature of the test to one that assesses active, rather than passive, memory. It would appear, then, that although passive memory for nonverbal information may be impaired in head-injured individuals, active memory for the same type of information is relatively preserved.

Working memory was found to be impaired in head-injured individuals during the screening interview but not the experiment itself, as evidenced by lower scores than the controls on the Listening Span Test, and scores comparable to controls on the Tower of Hanoi, respectively. Results from previous studies regarding the occurrence of working memory deficits following mild head injuries are equivocal: While some researchers suggest that working memory may be compromised long after a mild head injury (Newcombe et al., 1994; Baddeley et al., 1987), others have found no conclusive evidence (Gentilini et al., 1985; Gentilini, Nichelli & Schoenhuber, 1989). It is conceivable that varying types of head injuries, individual attributes and types of cognitive tests (e.g. verbal or nonverbal) may account for these differences in results.

Memory under conditions of interference and divided attention appeared to be impaired by mild head injuries, based on performance on the consonant trigrams test (CCC). Our findings that mildly head-injured individuals scored lower than controls on this test are in accordance with those of Stuss and colleagues (Stuss et al., 1985; Stuss, Stetham, Hugenholtz & Richard, 1989), who found that the CCC was sufficiently sensitive to differentiate concussed (mildly head-injured) subjects from their control group. Our finding adds further support to the claim that deficits in divided attention are associated with mild head injuries (Gronwall & Sampson 1974).

Deficits in long-term declarative memory were also apparent following mild head injuries, as indicated by lower scores of the head-injured individuals than controls on the

LMS-D. That this effect was apparent in mildly head-injured individuals extends previous findings that more severe head injuries may impair performance on the LMS-D (Mateer, 1992; Stuss et al., 1985) as well as other measures of long-term declarative memory (Mariadas et al., 1989; Benton & Grossman, 1982; Lezak, 1979). Our results support the assertion that memory is one of the cognitive functions most susceptible to impairment by closed head injury (Capruso & Levin, 1992; Levin et al., 1988).

It is important to note that although the present investigation found evidence for residual cognitive deficits in mildly head-injured individuals, many of the subjects classified as "mild" have received more than one concussion. This cumulative effect of concussion may explain why the present study found a deficit in some areas of cognitive functioning that other researchers either did not find, or found only with more severely head-injured patients. In fact, we have shown that a negative relationship exists between the number of head injuries and scores on the LMS-D in the saccharin condition, meaning that as the number of head injuries increases, the amount of information recalled is reduced. Although we are not aware of previous reports of this effect in sports other than boxing, our finding confirms the often-believed notion that repeated concussions can lead to memory loss. This finding also extends those from another study which found a cumulative effect of concussions on information processing speed: The rate at which individuals were able to process information, as assessed by the PASAT, was reduced more in individuals who had experienced two concussions than in those who had experienced only one (Gronwall & Wrightson, 1975). It would be interesting to know if a direct relationship exists between the number of mild head injuries and the degree of other types of cognitive impairment. In the present investigation, no such relationships were found but this may have been due to too few subjects.

Glucose was found to influence certain aspects of cognitive functioning but had different effects on the two groups: It enhanced long-term declarative memory and complex reaction time in head-injured individuals, while it impaired long-term declarative memory and enhanced accuracy on a complex reaction time task in controls. The effect of glucose on long-term declarative memory appeared to be related to individual blood-glucose regulation, which was found to differ between the head-injured and control groups.

Glucose selectively enhanced long-term declarative memory in the head-injured group, as evidenced by higher LMS-D scores in the glucose condition relative to the saccharin condition. In fact, head-injured individuals, who were shown to be slightly impaired on the LMS-D for the saccharin condition, actually retained as much, if not more, information than the control group for the glucose condition. This finding extends previous results in which glucose was shown to selectively enhance declarative memory in individuals with memory impairments, such as Alzheimer's patients and elderly individuals (Craft, Zallen & Baker, 1992; Gonder-Frederick et al., 1987; Hall et al., 1989; Manning, Hall & Gold, 1990; Manning, Parsons & Gold, 1992; Parsons & Gold, 1992; Manning, Ragozzino & Gold, 1993), by showing that glucose has similar effects on the same cognitive processes in individuals with mild head injuries.

Although glucose enhanced long-term declarative memory in those with head injuries, it impaired long-term declarative memory in the controls, as evidenced by lower

LMS-D scores in the glucose condition relative to the saccharin condition. Based on previous studies which found negligible memory-enhancing effects of glucose in young controls (Azari, 1991; Hall et al., 1989), we correctly predicted that controls would not show enhanced cognitive functioning by glucose. However, it was unexpected that glucose would impair long-term declarative memory. Earlier investigations obtaining similar findings (Craft et al., 1992; Craft et al., 1994) have suggested that individual glucoregulatory responses may be importantly implicated in the memory-enhancing effects of glucose; how quickly an individual's blood-glucose level returns to baseline may determine whether glucose will help or hinder memory.

In the present investigation, blood-glucose recovery was correlated with glucose-enhancement of memory and differed between the two groups. Both groups (head-injured, controls) had significantly higher blood-glucose levels at 15 minutes. However, at 50 minutes, blood-glucose remained high in the control group but dropped significantly in the head-injured group so that it was significantly lower than that of the controls. Thus, the head-injured group recovered from blood-glucose elevations at a faster rate than controls. Previous findings concerning the relationship between blood-glucose recovery and memory enhancement are inconclusive. While it has been suggested that no relationship exists between glucoregulatory control and memory performance in young adults (Hall et al., 1989), others have demonstrated that blood-glucose regulation is correlated with the effects of glucose on memory, though the direction of this correlation varies between investigations. In one study, subjects who had efficient blood-glucose regulation showed enhanced memory following ingestion of glucose, while those with less efficient blood-glucose regulation showed memory deterioration (Craft et al., 1992). Another study revealed that recall on a declarative memory measure was enhanced in older males with efficient blood-glucose recovery and in young males with poor recovery, while it was impaired in young males with good recovery (Craft et al., 1994). Differences in findings may well be due to differences in overall blood-glucose levels between the studies. The blood-glucose levels of individuals with good recovery in our study reached about the same peak levels (about 140 mg/dL) as did the poor recovery young subjects in the investigation by Craft et al. (1994). Hence, glucose enhancement of memory appears to be associated not only with the efficiency of recovery, but also optimal levels of blood-glucose. Blood-glucose levels too high or too low from this optimal level, then, will have a negligible, or even a detrimental, effect on memory. Thus, the results from these studies support the assertion that glucose enhances performance on long-term declarative memory tasks in an inverted-U response manner (Parsons & Gold, 1992) and suggest that optimal doses will depend on an individual's glucoregulatory mechanisms.

In the present study, glucose increased accuracy in the controls and improved reaction times of the head-injured individuals on a complex reaction time test (2-CH), as evidenced by better scores (i.e. higher for accuracy, lower for reaction time) on the glucose day relative to the saccharin day. Why glucose affected accuracy on this test in the controls and reaction time in the head-injured is not clear. Glucose did not appear to affect efficiency scores (a composite measure of reaction time and accuracy) for this task in either group. It is possible that while glucose enhanced accuracy, it compromised reaction time in control subjects, though this latter effect was not significant. Conversely, glucose improved reaction time but may have compromised accuracy in head-injured subjects, though this effect was not significant. That glucose affected different components of this cognitive task in the head-injured and control groups suggests that some aspect of blood-glucose regulation (and presumably, brain glucose utilization) was involved, albeit differently in the two groups.

Glucose did not appear to affect other aspects of cognitive functioning, including information processing speed, divided attention, passive memory for nonverbal information, working memory, noncontextual declarative memory (immediate or delayed), or immediate contextual declarative memory, in that there were no significant differences between performance in the glucose and saccharin conditions for the tests used to assess these cognitive functions (see Methods). It is possible that glucose had subtle effects on divided attention and information processing speed which were masked by significant practice effects on the CCC, and differences between the two versions of the SDMT, respectively. However, glucose was not found to influence information processing speed on other measures (SRT, 2-CH Efficiency, RM-CPT), and it did not influence short-term memory, so it is likely that glucose has a primary, rather than secondary (mediated by lower forms of cogntion), effect on memory. Our findings are consistent with those of previous studies in which the effects of glucose on cognition were primarily limited to performance on the LMS-D (Craft et al., 1994; Gonder-Frederick et al., 1987; Hall et al., 1989; Manning et al., 1988; Manning et al., 1990; Manning et al., 1992). This adds further support to the assertion that glucose does not affect overall cognitive function in young adults but instead selectively influences long-term declarative memory for contextual information. Nevertheless, we also found significant enhancement of accuracy (controls) and reaction time (head-injured) on a complex 2-choice reaction time task, which would tend to support previous findings that glucose may affect nonmemory functions, particularly measures of attention (Benton et al., 1994; Benton & Sargent, 1992; Allen et al., 1996). Perhaps different glucose doses or idiosyncratic differences in blood-glucose regulation and corresponding brain glucose utilization can explain these differences in results. It is conceivable that glucose could potentially enhance all types of cognitive processes, given the optimal dose. As previously mentioned, Parsons and Gold (1992), posited that the dose-response curve of glucose enhancement of memory in elderly humans represents an inverted-U function, with optimal blood-glucose levels being about 150-175 mg/dL, although it may be somewhat lower in young healthy adults (D.L. Korol, personal communication, Dec. 7, 1995). Dose-response relationships of glucose effects on attention and nonmemory functions have not yet been determined but investigations of these functions appear to be warranted.

It was previously mentioned that glucose regulation occurred more rapidly in the head-injured group, as evidenced by significantly lower blood-glucose levels in the head-injured group than the control group at 50 min post-ingestion. Although it was expected that glucoregulatory processes would differ somewhat in the two groups, it is not clear why the head-injured individuals recovered faster from the glucose load. As our between-subjects factors were based on attribute variables (head-injured, nonheadinjured), we could not randomly assign subjects to groups. As a result, our groups may have differed from one another on other attributes. Although all subjects in our study were athletes, individuals with mild head injuries may have been more committed to the game of rugby (i.e. have played for a longer period of time, or play and train more intensely) and accordingly, were more physically fit than controls. This would explain the difference in glucoregulation between the two groups, as it has previously been reported that level of physical fitness is highly correlated with insulin-stimulated glucose utilization (Rosenthal et al., 1983). It does not, however, elucidate if selective cognitive processes would be enhanced by glucose only in individuals with more efficient glucoregulatory abilities, regardless of head injury status. An investigation comparing glucose effects in individuals of varying fitness levels may help to determine whether the effects of glucose are primarily dependent upon glucoregulatory abilities, or if other attributes such as memory impairments associated with head-injuries are importantly implicated. Previous studies of glucose effects in elderly and Alzheimer's patients have asserted that individuals with memory impairments are most susceptible to glucose enhancement and that memory functions are highly correlated with glucoregulatory abilities (Craft et al., 1992; Hall et al., 1989; Manning et al., 1990). It is not known what role physical fitness plays in this relationship, as it was not accounted for in these investigations. However, future research examining the importance of this and other variables that affect glucoregulation, appear to be warranted.

Alternatively, possible differences in cognitive functioning and related brain glucose metabolism may partly explain the differences in glucoregulation and glucose effects on cognition in the two groups. Mild head injury has been associated with reduced information processing capacity and related susceptibility to fatigue (Gronwall, 1989). Presumably, head-injured individuals must work harder to perform at the same cognitive level as before the injury. This may translate into increased brain metabolism, or greater utilization of glucose by the brain. It has been suggested by Benton and colleagues (1994), who tested young adults on a difficult attention task, the Rapid Information Processing Task (RIPT) and subsequent word recall test, that subjects whose blood-glucose levels had fallen between the two tasks, were those whose brains had more efficiently taken up glucose to replace that used during the RIPT. This increased uptake supposedly replenished the intracellular glucose stores needed to facilitate memory on the word recall test. In our study, the Consonant Trigrams (CCC) test, which differentiated the control and head-injured groups in the saccharin condition, was given shortly after glucose ingestion. This test, along with those which followed it, may have placed more demands on information processing capacity in the head-injured group and produced a concomitant increase in cerebral glucose utilization. Hence, the drop in blood-glucose levels at 50 minutes post-ingestion may reflect increased uptake of glucose by the brain in the head-injured individuals. As the Logical Memory subtest was given approximately 45 to 50 minutes post-ingestion, it is conceivable that these subjects had optimal levels of brain glucose for long-term memory processes. The control subjects, however, may not have required the same levels of brain glucose to perform the preceding cognitive tasks and as a result, had more than optimal cerebral glucose levels for memory processes. This interpretation may help explain the findings in the present investigation, yet it should be regarded cautiously as much of it is based on speculation. Future studies examining the effects of cognitive processing on brain glucose levels and subsequent cerebral uptake of glucose in mildly head-injured and control subjects may offer some insight into our findings.

It is important to note the limitations associated with the present investigation, as they may temper the conclusions and implications that follow from our results. The first issue concerns the internal validity of the study. As two of our independent variables were based on individual attributes (head-injured, not head-injured), subjects were not randomly assigned to conditions. In addition, the criteria used to determine the occurrence of a head-injury is subject to debate. Subjects selected for the head-injured group were those who had experienced trauma to the head in the last 10 years and in which the injury resulted in one or more of the following: hospital admission, post-traumatic amnesia, altered level of consciousness, or fracture to the skull. Jennett (1975) reported that using these criteria will include injuries of varying severity, yet exclude many cases about which there is doubt about whether a head injury was sustained at all. Subjects selected for the control group were those that had not received a head injury, according to the previously mentioned criteria. All control subjects were rugby players from the same general population as the head-injured group, with the exception of four students. These students, who were involved in similar team sports, tended to have higher peak blood-glucose levels and less efficient glucoregulatory processes than most other members of the group. However, differences between the control and head-injured groups on blood-glucose measures and cognitive functions were still apparent even when these four subjects were excluded from analyses. These problems of internal validity limit our assertions regarding the effects of head-injury on cognition and glucoregulatory processes in that we cannot make claims of causation.

The second type of limitation concerns external validity. Subjects, who were selected from the population of rugby players at the University of Victoria, consisted of those who consented to participation. Because we did not randomly select these subjects from the general population, we are limited to generalizing our results, perhaps only to the population of university athletes (i.e. this group would include young, healthy individuals with higher education).

The third type of limitation concerns measurement issues. The degree of reliability and validity of the neuropsychological tests used in this study is not entirely known. However, there were practice effects associated with repeat administration of the CCC and differences between versions of the SDMT. In addition, data for the Tower of Hanoi task were missing for some subjects due to computer error. These measurement problems limit our assertions regarding the accuracy of our findings and question whether we were really assessing the cognitive functions that we intended to examine.

The fourth, and final, type of limitation concerns the type of statistical analyses selected. It can be argued that the statistics employed in this investigation may be too liberal. However, the present study may be viewed as a preliminary investigation, in that we explored the possibility that a number of cognitive functions may be impaired from mild head injuries. By using more liberal statistics, we were less likely to make a type II error which would eliminate potentially important variables from further study. While our results indicate that there was a difference between the groups on some of these tests, we acknowledge that these differences are marginal. This statistical concern tempers the importance and implications of our findings that cognitive performance is impaired in mildly head-injured individuals.

A number of interesting findings resulted from the present investigation. First, it was found that mild head injury is associated with subtle cognitive deficits, particularly those concerning passive memory for nonverbal information, working memory, divided attention and long-term contextual declarative memory. While it has been suggested that memory impairments may be secondary to an attention deficit (Gronwall, 1991), this does not appear to be the case in the present investigation, as our subjects were not impaired on a short-term memory task. This finding parallels those in which Alzheimer's patients and elderly individuals have problems retaining information (Hock, 1987) and corresponds with the contention that cognitive deficits are similar in head-injured individuals and Alzheimer's patients (Cope, 1986). Second, we found a cumulative effect of mild head injuries on long-term declarative memory, extending previous findings that number of concussions is directly related to reduced information processing speed (Gronwall & Wrightson, 1975). Third, it was found that glucose enhanced long-term declarative memory in the head-injured individuals. This extends previous findings that glucose selectively enhances long-term declarative memory in elderly (Craft et al., 1994; Gonder-Frederick et al., 1987; Hall et al., 1989; Manning et al., 1990; Manning et al., 1992; Parsons & Gold, 1992) and Alzheimer's patients (Craft et al., 1992; Manning et al., 1993) to include individuals with similar cognitive deficits resulting from mild head injuries. That glucose enhanced memory in the head-injured and impaired memory in controls may be due to differences in glucoregulatory responses, as the head-injured group recovered significantly faster from the glucose load than did the control group. While the reason for this difference in glucoregulation is not clear, it was suggested that differences in attributes, such as level of physical fitness, or differences in brain glucose metabolism may be importantly implicated. Fourth, it was found that while glucose improved reaction time in the head-injured individuals on a two-choice complex reaction time test, it enhanced accuracy in controls on the same task. This finding may be related to the differences in glucoregulation between the two groups.

The results of the present investigation suggest that cognitive deficits may result from sport-related head injuries. While these cognitive deficits appear to be quite subtle, they may become increasingly apparent with repeated injuries. Because varsity athletes must also attend to academic work, and cognitive deficits may impede this ability, it is important to prevent the occurrence of subsequent head injuries. In addition, methods of amelioration, such as keeping blood-glucose levels at an optimal level for memory functioning, may mitigate memory deficits.

Our results suggest that consolidation of declarative-type memories may depend on a glucose-mediated neurochemical process. Although the mechanisms underlying glucose's effects on memory are not entirely known, it has been proposed that circulating glucose levels might influence cerebral neurotransmitters such as acetylcholine (for a review, see Gold, 1991). Recent evidence suggests that glucose facilitates acetylcholine synthesis particularly in the hippocampus (Messier et al., 1991), a brain structure strongly implicated in the storage and retrieval of new memories (Squire & Zola-Morgan, 1991). Thus, the effects of glucose may be primarily limited to hippocampal mediated cognitive functions. An important implication of our findings is that methods of pharmaceutical therapy that alleviate long-term declarative memory problems in Alzheimer's patients and the elderly, may have a similar effect in mildly head-injured individuals.

A more general implication of the present findings is that eating habits (i.e. time since last meal) may play an important role in cognitive processes. Whether this effect is dependent upon glucoregulatory responses, head injury status, or baseline level of cognitive functioning is not clear but it is suggested that future studies should further examine the relationship among these variables to determine which are most important.

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Appendix A

CONSENT FORM FOR PARTICIPATION IN THE STUDY ENTITLED, "THE EFFECTS OF SWEETENERS ON INFORMATION PROCESSING"

I understand that during this interview, I will be asked about my medical history, including questions regarding my history of head injury and any related problems that may have resulted.

I understand that my participation is completely voluntary and that I can withdraw from the study at any time without explanation.

I understand that any data collected in this study will remain confidential; interview results and questionnaires will be kept in a locked room. Furthermore, I understand that my name will not be attached to any published results and that my anonymity is guaranteed by using code numbers to identify the results obtained from individual subjects.

I understand that the tests given in these sessions are for research purposes and are not intended to provide a neuropsychological assessment of current intellectual abilities. I also understand that these tests are not for therapeutic or rehabilitative purposes.

I understand that whether I participate or choose not to participate will have no bearing on my grade / employment status / academic standing / job.

Date: ________________________

Signature: ________________________

Experimenter: ________________________

Appendix B

HEALTH / MEDICAL QUESTIONNAIRE

1. Do you normally eat breakfast?

2. If you answered yes to question 1, at what time do you typically eat?

3. Do you have phenylketonuria, diabetes, hypoglycemia or any other blood sugar problems?

4. Do you have any adverse reactions to natural or artificial sweeteners (saccharin, aspartame)?

5. Do you have any food or drug allergies?

6. Are you currently on any medications?

7. Do you have any other health conditions that we should be aware of before commencing this study?

Appendix C

STRUCTURED INTERVIEW

i. How old are you?
ii. How many years of education?
1. Have you ever had a head injury? More than once?
2. How long ago was/were the injury/injuries?
3. To the best of your ability, please recount the details of the injury (if more than one, please describe the one you believe was the most severe).
4. Were you admitted to the hospital following a head injury? If so, for how long?
5. Were you unconscious for any length of time following the injury? If so, how long?
6. Did you have any periods of disorientation (inability to remember who had visited you or what was said)? Roughly how long was this period?
7. Were there any other complications from this injury (ie. fractured skull, hematoma)?

Please rate the following on a 7 point scale (1=always, 2=very often 3=often, 4=sometimes, 5= not very often, 6=rarely, 7=never)

9. Do you find it difficult to follow directions?
10. Is it hard to do more than one thing at the same time?
11. When talking, do you lose the point you wanted to make?
12. Does conversation, music or other sound tend to disturb your concentration ?
13. Do you find that you tend to go from task to task without finishing?
14. Do you forget what you have just been told?
15. Do you misplace your belongings?
16. Do you forget events, e.g. what you did earlier today or yesterday?
17. Do you forget to do important things?
18. Do you need to write things down to avoid forgetting or do others need to remind you?
19. Does it seem to take a long time for you to learn new materials ?
20. Does it seem to take effort and/or a long time to recall the words for common objects, the names of people you know, familiar telephone numbers and addresses, etc.?
21. In general, do you find your university education demanding?
22. Are there any other long-term consequences you'd like to mention?

Appendix D

LISTENING SPAN TEST (Sample)

INSTRUCTIONS

In this task you will be asked to answer questions about simple sentences that will be orally presented, while simultaneously trying to remember the final word from each of the sentences. After you hear each sentence, you should mark the correct answer to the question that is written in your test booklet. When you hear the word RECALL, please turn the page and write the last word from each of the sentences in the order in which they were presented.

Please look at the example. You will hear simple sentences like: "The boy ran with the dog." The question on the response form is "who ran?", and therefore you should place an X next to the alternative "boy" on the form. You might then hear another sentence like: "last night, Tom went to school." Because the correct answer to the question "When" is "last night", you should place an X next to that alternative on the form.

When you hear the word RECALL, you should turn the page and write the final word from each of the sentences that I read to you. In this example, you should write the words "dog" and "school" because they are the final words of the sentence that I read to you.

Since we are interested in how well you can remember while performing simple tasks, we ask that you not write the to-be-remembered words until you hear the word RECALL. Please mark only the correct answer to the question on the answer sheet immediately after hearing the sentence. After hearing the word RECALL, you should turn the page and write the FINAL WORDS, <u>not the answer to the question</u>, in the order in which they were presented.

You may find at times that the task seems to move fairly rapidly. If it becomes difficult for you to answer the questions and remember the words, concentrate on answering the questions correctly.

ARE THERE ANY QUESTIONS BEFORE WE BEGIN?

LSPAN - SET A

TURN TO THE FIRST PAGE

We will now begin the trials with **one** sentence.

TRIAL 1:

READY

After dinner, the chef prepared dessert for her guests.

TURN THE PAGE AND RECALL (6 seconds)
TURN BACK TO THE PREVIOUS PAGE (3 seconds)

TRIAL 2:

READY

Everyone in the stadium felt cold.

TURN THE PAGE AND RECALL (6 seconds)
TURN BACK TO THE PREVIOUS PAGE (3 seconds)

TRIAL 3:

READY

The people on the airplane had never flown before.

TURN THE PAGE AND RECALL (6 seconds)

LSPAN - SET A

TURN TO THE NEXT PAGE (5 seconds)

We will now begin the trials with **two** sentences.

TRIAL 1:

READY

The fans at the football game wore hats and scarves.
The Grants told their guests from France and Italy about the city.

TURN THE PAGE AND RECALL (7 seconds)
TURN BACK TO THE PREVIOUS PAGE (5 seconds)

TRIAL 2:

READY

Last year we had a cold winter.
The passengers on the train were happy.

TURN THE PAGE AND RECALL (7 seconds)
TURN BACK TO THE PREVIOUS PAGE (3 seconds)

TRIAL 3:

READY

In the library, the girl read her book.
The basketball team won the championship last year.

TURN THE PAGE AND RECALL (7 seconds)

LSPAN - SET A

TURN TO THE NEXT PAGE (5 seconds)

We will now begin the trials with **three** sentences.

TRIAL 1:

READY

Last fall the farmers had a good harvest.
The children in the car wanted to stop for ice cream.
The baseball player hit the ball over the fence.

TURN THE PAGE AND RECALL (8 seconds)
TURN BACK TO THE PREVIOUS PAGE (3 seconds)

TRIAL 2:

READY

The maid usually washes the clothes in the afternoon.
The woman planted pansies on her patio.
The iron gate clanged shut.

TURN THE PAGE AND RECALL (8 seconds)
TURN BACK TO THE PREVIOUS PAGE (3 seconds)

TRIAL 3:

READY

The door that leads to the basement was locked.
A bear looks for food in the woods.
The bald eagle soars over the trees.

TURN THE PAGE AND RECALL (8 seconds)

LISTENING SPAN

In this task you will be asked to answer questions about simple sentences that will be orally presented, while simultaneously trying to remember the final word of each sentence. After you hear each sentence, you will be asked a question. You should mark the correct answer to the question on the answer sheet. When you hear the word "RECALL", please turn the page and write the last word from each of the sentences in the order in which they were presented.

EXAMPLE:

	Answer Sheet
(you will hear)	(You should mark)
THE BOY RAN WITH THE DOG	Who ran? _X_boy __man __girl
LAST NIGHT, TOM WENT TO SCHOOL	When? __now __yesterday _X_last night
RECALL	(turn page)
	RECALL
	dog
	_school

Please mark the correct answer on the answer sheet immediately after hearing the sentence. You should only write the final words of the sentences (not the answer to the question) after hearing the word "RECALL".

PLEASE DO NOT TURN THE PAGE UNTIL INSTRUCTED TO DO SO.

<u>**Level 1**</u>

Trial 1

What did the chef prepare?
______fish
______dessert
______salad

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

new page

<u>**Recall**</u>

Trial 1

______

<u>Level 1</u>

Trial 2

Where was everyone?
______at home
______at the rink
______sin the stadium

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

new page

<u>Recall</u>

Trial 2

______

<u>Level 1</u>

Trial 3

Where are the people?
______on the train
______on the airplane
______on the boat

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

<u>*new page*</u>

<u>Recall</u>

Trial 3

______

<u>Level 2</u>

Trial 1

Where were the fans?
______at the football game
______at the rink
______at home

Where were the guests from?
______Spain
______England
______France

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

______________________ *new page* ______________________

<u>Recall</u>

Trial 1

______

______

<u>Level 2</u>

Trial 2

When?
______last year
______this year
______next year

Where were the passengers?
______on the plane
______on the boat
______on the train

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

new page

<u>Recall</u>

Trial 2

______

______

Level 2

Trial 3

Where did she read?
______library
______bookstore
______school

What did the team win?
______championship
______game
______tournament

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

______________________________*new page*______________________________

Recall

Trial 3

______

______

<u>Level 3</u>

Trial 1

When?
______this fall
______last fall
______next fall

Where were the children?
______on the train
______on the boat
______in the car

What did the player hit?
______the ball
______the jackpot
______the backstop

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

new page

<u>Recall</u>

Trial 1

______

______

______

<u>Level 3</u>

Trial 2

What does the maid do?
______iron clothes
______wash clothes
______wash floors

What did the woman plant?
______pansies
______grass
______daffodils

What clanged?
______door
______window
______gate

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

new page

<u>Recall</u>

Trial 2

______

______

______

<u>Level 3</u>

Trial 3

Where did the door lead?
______closet
______attic
______basement

What does the bear look for?
______trees
______food
______caves

What soared?
______the kite
______the eagle
______the plane

PLEASE WAIT UNTIL YOU HEAR THE WORD "RECALL" BEFORE TURNING THE PAGE

______________________________________ *new page* ______________________________________

<u>Recall</u>

Trial 3

______

______

______

Appendix E

CONSENT FORM FOR PARTICIPATION IN THE STUDY ENTITLED, "THE EFFECTS OF SWEETENERS ON INFORMATION PROCESSING"

I understand that this research project is studying the effects of sweeteners on information processing. I understand that I will be asked to refrain from eating or drinking anything (except water) after 12:00 midnight before each of the three early morning testing sessions. I understand that I will be asked to drink a 16 ounce fruit-flavoured beverage, sweetened with artificial and/or natural sweeteners upon arriving at the test session and my blood will be taken 3 times per session. I understand that this procedure, which has been described as being virtually painless, involves pricking the finger to obtain one drop of blood. I understand that I will then be asked to complete a series of attention and memory tests.

I understand that my participation is completely voluntary and I can withdraw from the study at any time, even within a session, without explanation, and that any data collected from me up to that point will not be used.

I understand that any data collected in the study will remain confidential; experimental results and questionnaires will be kept in a locked room. Furthermore, I understand that my name will not be attached to any published results and that my anonymity is guaranteed by using code numbers to identify the results obtained from individual subjects.

I understand that the tests given in these sessions are for research purposes and are not intended to provide a neuropsychological assessment of current intellectual abilities. I also understand that these tests are not for therapeutic or rehabilitative purposes.

I agree to not reveal information about this study to other potential participants until the entire study has been completed (i.e. all participants have been tested). I understand that I can receive a summary of the results and conclusions.

I understand that whether I participate or choose not to participate will have no bearing on my grade / employment status / academic standing / job.

Date: ______________________________

Signature: ______________________________

Experimenter: ______________________________

Appendix F

PAIRED ASSOCIATES

Verbal Paired Associates II
(Delayed Recall)
Version 01-MJG

Stimulus Word (& Correct R)	Con	Abs
FORK-(Caterpillar)	______	
BEGGAR-(Village)	______	
BELIEF-(Instance)		______
BOUQUET-(Elephant)	______	
CHANCE-(Fact)		______
FIRE-(String)	______	
ADVANTAGE-(Occasion)		______
BLISTER-(Alligator)	______	

Verbal Paired Associates II
(Delayed Recall)
Version 02-MJG

Stimulus Word (& Correct R)	Con	Abs
HAMMER-(Refrigerator)	______	
BLOOD-(Ocean)	______	
FAULT-(Moment)		______
GRASS-(Piano)	______	
EXCUSE-(Thought)		______
ROCKS-(Wine)	______	
TRUTH-(Amount)		______
PENCIL-(Strawberry)	______	

Appendix G

Debriefing

Tests:

The tests used in this study are experimental measures so that we cannot really define what is a "normal" score. Instead, they are used to compare your performance under 2 different conditions (artificial vs. natural sweeteners).

There is nothing "hidden" with regards to what the tests measure. That is, they are not designed to assess things like personality, intelligence or social skills. Rather, these tests measure pretty much what they may have seemed to you to be measuring. For example, the paragraph story and the word pair tests were used to assess memory, while the symbol digit test was used to assess information processing speed.

- Do you have any questions about the tests or the testing procedure?

Performance:

- With respect to the first two days of testing, did you feel that you could think more clearly on one day versus the other?
- If yes, which day and do you have any possible explanations (i.e. weather, amount of sleep, mood, etc.)?
- Do you think this was reflected in your performance?
- With respect to the 24 hour recall tests given at the beginning of the second and third testing sessions,do you feel that you did better on one day versus the other?
- If yes, which day, and why do you suppose that you performed differently on these two days?

Drinks:

- How did you feel after drinking the drink on day 1?
- How did you feel after drinking the drink on day2?
- Did you notice any difference in how you felt after drinking drink 1 versus drink 2?
- Did the drinks taste similar to you?
- One of the drinks was sweetened with artificial sweetener, while the other was sweetened with a natural sweetener. Which do you think was which?

- Do you have any other questions?

When this study has been completed (i.e. all the participants have been tested) you may obtain a summary of the results and conclusions. You can do this by contacting me at 472-2631 or Dr. Ron Skelton (Psychology professor) at 721-8711.

(Thank for participation, get participant to sign name and give $10)

VITA

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Howard Petch Graduate Scholarship	1994
B.C. Psychological Association Gold Medal	1993
Governor General's Medal	1993
NSERC Undergraduate Research Award	1993
Nellie Gillespie Prize	1993
Alumni Undergraduate Scholarship	1992
W.H. Gaddes Scholarship	1992
Rotary Club of Saanich Award	1992
Percy H. Elliot Memorial Scholarship	1992
Howard Petch Scholarship	1992
UVic President's Entrance Scholarship	1991
Northwood Pulp & Timber Ltd. Scholarship	1991
Real Estate Endowment Award	1990
Knight's of Columbus Award	1990
University Women's Club Scholarship	1990
CNC Student's Assn. Scholarship	1989

Title of Thesis:

Glucose Enhances Long-Term Declarative Memory in Mildly Head-Injured Varsity Rugby Players

Author [redacted]

Jacqueline Adele Tutte
April 14, 1997