Short-Term, Delayed, and Working Memory Are Impaired During Hypoglycemia in Individuals With Type 1 Diabetes

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OBJECTIVE — To examine the effects of acute insulin-induced hypoglycemia on short-term, delayed, and working memory in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A hyperinsulinemic glucose clamp was used to maintain arterialized blood glucose level at either 4.5 mmol/l (euglycemia) or 2.5 mmol/l (hypoglycemia) on two separate occasions in 16 adults with type 1 diabetes. The participants completed tests of immediate and delayed verbal memory, immediate and delayed visual memory, and working memory during each experimental condition. Two other mental tests, the Trail Making B Test and the Digit Symbol Test, were also administered.

RESULTS — Performance in tests of immediate verbal and immediate visual memory was significantly impaired during hypoglycemia. The effect of hypoglycemia on working memory and delayed memory was more profound. Performance in the nonmemory tests, the Trail Making B Test, and the Digit Symbol Test also deteriorated during hypoglycemia.

CONCLUSIONS — All of the memory systems examined in the present study were affected significantly by acute hypoglycemia, particularly working memory and delayed memory. Mild (self-treated) hypoglycemia is common in individuals with insulin-treated diabetes; therefore, these observed effects of hypoglycemia on memory are of potential clinical importance because they could interfere with many everyday activities.

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Hypoglycemia is a common adverse effect of treatment with insulin in individuals with diabetes (1,2). Acute neuroglycopenia causes rapid deterioration of cognitive function in humans with and without diabetes (3). Complex and attention-demanding tasks, as well as those that require a rapid response, are more affected by neuroglycopenia, whereas simple motor and cognitive tasks are relatively preserved. In general, results of tests that involve attention, concentration, psychomotor skills, accessing of long-term memory, and ability to ignore distracting information deteriorate when arterial blood glucose level declines below ~3.0 mmol/l (4–9).

Memory is one of the most important cognitive domains with respect to everyday function and is the process of storing, encoding, and retrieving information. Different forms of memory are recognized, including sensory, short-term, long-term, and working memory (10). In sensory memory, representations of the physical features of a stimulus are stored for a very brief time (≤1 s), and it is difficult to distinguish from the process of perception. The deleterious effect of hypoglycemia on this memory system has been demonstrated in previous studies conducted in our center (11–14). It seems that the principal function of sensory memory is to retain information for a period of time sufficient to allow its transfer to short-term memory. Short-term memory refers to the function that temporarily retains stimuli that have just been perceived. Its capacity is limited in terms of the number of items that can be stored and lasts for ~20 s. Through repetition, information may be transferred from short-term memory to long-term memory. Long-term memory refers to information that is represented on a more permanent basis. Unlike short-term memory, long-term memory has no known limits to capacity and is relatively durable.

Working memory is a short-term memory system that allows concurrent retention and manipulation of information (15). It is used for thinking about what is already known and for deriving conclusions on the basis of that knowledge; therefore, working memory is fundamental to successful completion of many activities. For example, it is used to remember what has been said at the beginning of a sentence and retain this until the sentence has been completed and is essential for the calculation of mental arithmetic. It allows spatial relations to be updated in our mental map as we move through a new geographical location.

Few studies have examined the effects of acute hypoglycemia on memory function, other than by including a heterogeneous assortment of memory measures as part of a larger battery of cognitive tests. In some studies (6,7,9,16,17), memory functions were impaired during acute hypoglycemia, whereas in other studies (8,18,19), memory was apparently unaffected. Variability of results may relate to

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Abbreviations: AVLT, Auditory Verbal Learning Test; BVRT, Benton Visual Retention Test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

methodological differences. Many studies are limited by small sample size, application of a limited selection of tests, and inadequate ascertainment of biomedical and psychosocial variables that could affect the results. The method of induction of hypoglycemia has also varied between studies, with differing methods of blood sampling (e.g., arterialized or venous blood). A common methodological error has been induction of a stepwise decrease in blood glucose level with estimation of cognitive function during the final 30 min of each blood glucose plateau, thus confounding glucose level with practice effects. In addition, in a study by Holmes et al. (18), the blood glucose nadir was only 3.3 mmol/l, and the studies by Widom and Simonson (8) and Harrad et al. (19) used only a single test to assess memory function. These factors may also help explain the discrepancy in results between different studies.

In our laboratory, a more comprehensive examination of the effects of moderate acute hypoglycemia on memory performance in healthy nondiabetic humans demonstrated impairment of all memory systems; working memory and delayed memory were most susceptible to the effects of neuroglycopenia (20). The present study was designed to investigate the effects of experimentally induced hypoglycemia on verbal and nonverbal tests of short-term, delayed, and working memory in adults with type 1 diabetes, many of whom frequently have mild (self-treated) hypoglycemia.

RESEARCH DESIGN AND METHODS

Subjects

A total of 16 adults with type 1 diabetes (9 men, 7 women) were studied. Subjects were recruited from the diabetes outpatient clinics at the Royal Infirmary of Edinburgh. The median (range) data for the study participants were as follows: age 28.5 years (20.0–38.2), BMI 23.9 kg/m^2 (20.1–24.8), duration of diabetes 4.5 years (1.2–8.4), HbA_{1c} 8.2% (6.9–8.7), and insulin dose 0.65 U/kg (0.25–1.1). HbA_{1c} was measured by high-performance liquid chromatography (Variant II Hemoglobin Testing System; Biorad Diagnostics, Hercules, CA) (nondiabetic reference range 4.3–6.5%). None of the participants had a history of hypertension or chronic disease, previous head injury, seizure, blackouts, alcohol or drug abuse, or psychiatric illness. They had no intercurrent illness and were not taking any regular medication (except for insulin and oral contraceptives). Subjects were excluded from the study if they had any evidence of microvascular disease. Presence of retinopathy was ascertained by ophthalmoscopy, neuropathy was determined by clinical examination, and nephropathy was defined by presence of microalbuminuria. Subjects were excluded if they had a history of impaired awareness of hypoglycemia or had suffered an episode of hypoglycemia in the 48 h preceding the study. All subjects gave written informed consent for participation in the study.

Study design

Each subject participated in two laboratory sessions that were separated by at least 2 weeks. The study was conducted in the Department of Diabetes at the Royal Infirmary of Edinburgh. A modified hyperinsulinemic glucose clamp (21) was used to maintain blood glucose at a predetermined level. In the euglycemia condition, the arterialized blood glucose concentration was maintained at 4.5 mmol/l and hypoglycemia was not induced. In the hypoglycemia condition, the glucose concentration was decreased to 2.5 mmol/l. The subjects were not informed which experimental condition of the study was being undertaken on each occasion, and the two experimental sessions were performed in a randomized and counterbalanced fashion.

Procedure

Each session commenced at 8:00 A.M. after a 10- to 12-h overnight fast, and the subjects omitted their morning dose of insulin. An intravenous cannula for regular blood sampling was inserted retrogradely into a vein on the dorsum of the nondominant hand, which was placed in a heated blanket to arterialize the venous blood. A second intravenous cannula was inserted into a vein in the antecubital fossa of the same arm for infusion of human soluble insulin (Humulin S; Eli Lilly, Indianapolis, IN) and 20% dextrose. Intradermal lidocaine (1%) was used for insertion of the cannulae. Insulin was infused at a constant rate of 60 mU $\cdot$ m^{-2} $\cdot$ min^{-1} using an IMED Gemini PCI pump (Alaris Medical Systems, San Diego, CA). A variable intravenous infusion of 20% dextrose was given simultaneously. The rate of dextrose infusion was varied according to the arterialized blood glucose concentration, which was measured at the bedside using the glucose oxidase method (2300 Stat; Yellow Springs Instrument, Yellow Springs, OH). Blood glucose concentration was measured every 3 min until a stable level was achieved and then at 5-min intervals.

In each study condition, the arterialized blood glucose concentration was stabilized initially at 4.5 mmol/l (baseline) for a period of 30 min. In the euglycemia condition, the blood glucose concentration was maintained thereafter at 4.5 mmol/l throughout the study. In the hypoglycemia condition, blood glucose was lowered over a 20-min period to 2.5 mmol/l. The blood glucose concentration was maintained at the predetermined target level for an additional 10 min before commencement of the cognitive tests and was maintained at this level for an additional 70 min during administration of the tests. At the end of the hypoglycemia condition, the blood glucose level was restored to 4.5 mmol/l. Subjects were given a meal after completion of each study.

Cognitive function tests

Tests of immediate and delayed verbal memory, immediate and delayed visual memory, and tests of working memory were administered during the study conditions. In addition to the memory tests, the Trail Making B Test and the Digit Symbol Test were also administered. These tests were used to confirm the effect of hypoglycemia on cognitive function, as has been shown in previous studies (9,11,12,17,22).

Verbal memory tests

Auditory Verbal Learning Test: immediate and delayed. The Auditory Verbal Learning Test (AVLT) is a test of immediate memory capacity, retrieval efficiency, and learning. The delayed component measures longer-term retention (23). It consists of a list of 15 words that are read to the subject at a rate of one word per second. The subject is asked to try to recall words immediately in any order from the list. This procedure is repeated five times. The total of words remembered correctly is designated as the "immediate" score. Each subject is instructed to try to remember the words on the list and is

informed that recall of words from the list will be requested after a period of 1 h. The "delayed" score is the number of words that are recalled correctly at that time. The percentage of words that were retained from the immediate to the delayed score ("percent retained") was also calculated.

Logical Memory Test: immediate and delayed. The Logical Memory Test, a subtest from the Wechsler Memory Scales (24), is a test of verbal learning. It measures immediate free recall after auditory presentation and delayed recall. The subject is asked to recount a short story immediately after it is read to them, to remember the story, and to recall it again after a 1-h delay. The story incorporates 25 specific points or "story elements," each of which the subject must recall to obtain credit. The immediate and delayed scores are the sum of the number of points remembered by the subject during immediate and delayed recall, respectively. From these scores, the percentage of information retained from the immediate to the delayed presentation was also calculated.

Visual memory tests

Visual Reproduction Test: immediate and delayed. This Wechsler Memory Scales subtest measures immediate and delayed recall after nonverbal, visual presentation (24). A design (line drawing) is presented to the subject, who is allowed to study the design for 10 s. The design is then removed and the subject is instructed to draw the design from memory. The next design follows, for a total of five. The subject is asked to draw the designs again after a delay of at least 1 h. The designs are scored according to their accuracy. The total score is the sum of the scores of all five designs. Immediate and delayed scores are calculated separately, and from these the percent retained score was also derived.

Benton Visual Retention Test. The Benton Visual Retention Test (BVRT) is a test of immediate visual recall. A series of 10 designs of increasing complexity are presented to the subject, the designs are removed, and the subject is then asked to draw the designs from memory (25). The test is scored according to the accuracy with which the designs are drawn. The total score is the sum of the scores of all 10 designs.

Working memory tests

Working Digit Span Test: forward and backward. In the digit span test, a series of lists of numbers is presented verbally to the subject. The standard Wechsler Memory Scales Digit Span Test (24) was modified for this experiment to test working memory more fully. The subjects were asked to recall the numbers in ascending numerical order (forward) or reverse numerical order (backward). For example, for the sequence 2-6-1-5-3, the correct response for working digit span forward is 1-2-3-5-6, and for working digit span backward, the correct response is 6-5-3-2-1. The test score is the number of lists that are remembered correctly.

Letter/Number Sequencing Test. In the Letter/Number Sequencing Test from the Wechsler Memory Scales, a series of lists of numbers mixed with letters is presented verbally (24). The subject must recall the list, stating the numbers in ascending numerical order followed by the letters in alphabetical order. For example, for the sequence 2-D-6-A-1-G, the correct response is 1-2-6 A-D-G. The test score is the number of lists that are remembered correctly.

Validation Span Test. In the Validation Span Test from the Kyllonen's Cognitive Abilities Measurement battery (26), the subject is presented visually with a simple arithmetical problem. The subject is required to perform the calculation and to determine whether the sum is correct or incorrect. On the left side of the page, adjacent to the problem, an isolated and unrelated number is placed. In addition to performing the simple mental arithmetic, the subject must remember this isolated number. Each problem is presented for 5 s. The problems are presented in sets of three, four, and five. After completion of each set, the subject must recall the isolated left-sided numbers in the correct order. The score is based on how many of the isolated numbers are remembered correctly. An example of a set of three is given below:

5 $3 + 2 - 1 = 4$ (correct)
2 $1 - 5 + 8 = 7$ (incorrect)
3 $2 + 4 + 6 = 12$ (correct)

For this example, the correct sequence of numbers is 5-2-3.

Parallel versions of the Logical Memory Test, AVLT, BVRT, and Validation Span Test are available; in the present study, these were used to minimize a learning effect between the two study conditions. Throughout the study, the battery of tests was performed in a fixed order.

Other mental tests

Trail Making B Test. The Trail Making B Test from the Halstead Reitan battery (27) assesses complex visual scanning and has a motor component that measures visual conceptual and visual motor tracking. An electronic version of the test, performed on a handheld computer, was used for this study (28). In this test, the subject is presented with a grid containing randomly positioned numbers and letters. The subject is to connect consecutive numbers in numerical order and consecutive letters in alphabetical order, alternating between numbers and letters. The score is the time taken to complete the task.

Digit Symbol Test. This Digit Symbol Test from the Wechsler Adult Intelligence Scale is a test of coding performed at speed. It consists of four rows containing at total of 100 small blank squares, each paired with a randomly assigned number from 1 to 9. Above these rows, a printed key is shown, which pairs each number with a different symbol. The subject is asked to fill in as many of the blank squares with the appropriate symbol that matches the number above the box, in a time limit of 120 s (29). The score is the number of squares that are successfully completed within 120 s.

Symptoms of hypoglycemia

The Edinburgh Hypoglycemia Scale (30), a validated subjective self-rating questionnaire, was used to document the common symptoms of hypoglycemia experienced by the subjects during the two studies. The symptoms of hypoglycemia were classified as autonomic (hunger, palpitations, sweating, shaking), neuroglycopenic (drowsiness, confusion, inability to concentrate, speech difficulty, blurred vision), and nonspecific (nausea, headache). Each symptom was graded using a Likert Scale of 1 (not present) to 7 (very intense).

Statistical analysis

The results were analyzed independently for each memory test. A general linear model (repeated-measures ANOVA) was

Table 1—*Results of tests of memory function during euglycemia and hypoglycemia in 16 adults with type 1 diabetes*

Memory system	Subtest	Euglycemia	Hypoglycemia	*P* value	η^2
Immediate verbal memory					
	Immediate Logical Memory Test	26.8 ± 4.8	21.3 ± 6.9	0.008	0.41
	Immediate AVLT	39.4 ± 7.7	34.0 ± 5.1	0.002	0.49
Immediate visual memory					
	Benton Visual Retention Test	6.5 ± 1.7	4.7 ± 1.5	0.007	0.42
	Visual Reproduction Test	81.3 ± 7.2	78.2 ± 9.5	0.093	0.19
Delayed memory					
	Delayed Logical Memory Test	13.6 ± 2.1	6.1 ± 3.7	<0.0001	0.83
	Percent retained	78.4 ± 6.0	47.0 ± 21.3	<0.0001	0.73
	Delayed AVLT	9.1 ± 1.9	5.3 ± 1.9	<0.0001	0.68
	Percent retained	79.1 ± 6.9	47.8 ± 16.0	<0.0001	0.78
	Delayed Visual Reproduction	15.9 ± 8.7	7.1 ± 7.3	0.002	0.52
	Percent retained	18.6 ± 9.8	9.1 ± 9.0	0.004	0.46
Working memory					
	Validation Span Test	20.7 ± 2.3	14.9 ± 2.2	<0.0001	0.92
	Modified Digit Span Forward Test	9.56 ± 2.4	8.6 ± 1.4	0.06	0.23
	Modified Digit Span Backward Test	8.3 ± 1.9	7.2 ± 1.2	0.02	0.33
	Letter/Number Sequencing Test	11.8 ± 1.9	9.7 ± 1.6	0.0001	0.57

Data are means ± SD.

used; order of session (euglycemia-hypoglycemia or hypoglycemia-euglycemia) was a "between subjects" factor, and condition (euglycemia or hypoglycemia) was a "within subjects" factor. A P value <0.05 was considered significant. Effect size was calculated using η^2. An η^2 score of 0.25–0.5 was considered a moderate effect size. All analyses were performed using SPSS statistical software (version 10.0 for Windows; SPSS, Chicago, IL).

RESULTS — A stable blood glucose plateau was achieved during each study condition. The mean (SD) arterialized blood glucose concentration during the euglycemia condition was 4.55 mmol/l (0.18) and during the hypoglycemia condition was 2.51 mmol/l (0.08). Statistical analysis showed that no significant order effects had occurred for any of the outcome variables of this study and no significant sex differences were evident.

Symptoms

Results of the hypoglycemia symptom questionnaires confirmed that scores for autonomic ($P < 0.0001$), neuroglycopenic ($P = 0.001$), and general malaise ($P = 0.008$) symptoms were all significantly elevated during hypoglycemia compared with baseline euglycemia and were unchanged from baseline levels during the euglycemia study condition.

Digit Symbol and Trail Making B Tests

During hypoglycemia, the time taken to complete the Trail Making B Test increased significantly from a mean (SD) of 33.7 s (7.7) during euglycemia to 54.0 s (10.7) during hypoglycemia ($P < 0.0001$, $\eta^2 = 0.68$). The mean (SD) score of the Digit Symbol Test declined from 73.5 (11.2) during euglycemia to 62.9 (16.9) during hypoglycemia ($P = 0.001$, $\eta^2 = 0.57$).

Tests of memory

The results of the memory function tests are summarized in Table 1.

Immediate verbal memory. Acute hypoglycemia caused a significant deterioration in immediate verbal memory as assessed by the AVLT ($P = 0.002$, $\eta^2 = 0.49$) and the Logical Memory Test ($P = 0.008$, $\eta^2 = 0.41$).

Immediate visual memory. The BVRT score decreased during hypoglycemia ($P = 0.007$, $\eta^2 = 0.42$). By contrast, the score for the visual reproduction test did not decrease significantly ($P = 0.093$).

Delayed verbal memory. Scores for both the Delayed AVLT ($P < 0.0001$, $\eta^2 = 0.68$; percent retained, $P < 0.0001$, $\eta^2 = 0.78$) and the Delayed Logical Memory Test ($P < 0.0001$, $\eta^2 = 0.83$; percent retained, $P < 0.0001$, $\eta^2 = 0.73$) were significantly worse during hypoglycemia.

Delayed visual memory. During hypoglycemia, a significant decrement was observed in the Delayed Visual Reproduction Test ($P = 0.002$, $\eta^2 = 0.52$; percent retained, $P = 0.004$, $\eta^2 = 0.46$).

Working memory. The Working Digit Span Backward Test ($P = 0.02$, $\eta^2 = 0.33$), Letter/Number Sequencing Test ($P = 0.001$, $\eta^2 = 0.57$), and Validation Span Test ($P < 0.0001$, $\eta^2 = 0.92$) all demonstrated a significant decrement during hypoglycemia. The Validation Span Test decreased from a mean (SD) score of 20.7 (2.3) during euglycemia to 14.9 (2.2) during hypoglycemia. However, performance in the Working Digit Span Forward Test was not significantly affected ($P = 0.06$, $\eta^2 = 0.23$).

CONCLUSIONS — Few previous studies have made a detailed examination of the effects of acute hypoglycemia on memory function in humans, with and without diabetes (8,9,16–18), and earlier studies have given inconsistent results. Using an identical study design, we have studied the effects of hypoglycemia in young, healthy, nondiabetic volunteers and demonstrated a profound impairment in memory function at a blood glucose level that was similar to the present study (2.5 mmol/l) (20). In view of the frequency with which mild hypoglycemia is experienced by individuals with insulin-treated diabetes, the present study

has examined the effects of acute hypoglycemia on a wide range of memory functions in a group of adults with type 1 diabetes who had no evidence of significant vascular complications.

The present study has demonstrated that in adults with type 1 diabetes, acute moderate hypoglycemia caused a marked deterioration in performance in tests of short-term, delayed, and working memory, for both verbal and nonverbal material; working memory and delayed memory were most strongly affected (according to analysis of effect size). In addition, performance in the Trail Making B Test and the Digit Symbol Test was impaired significantly during hypoglycemia. This is consistent with previous observations (9,11,12,17,22) and confirms that the degree of hypoglycemia achieved was sufficient to affect other domains of cognitive function.

Short-term memory was significantly disrupted by hypoglycemia in the present study. The effect of hypoglycemia on short-term verbal memory, assessed by the AVLT and the Logical Memory Test, and short-term visual memory, assessed by the BVRT, was profound; performance on all three tests was significantly impaired. Earlier studies (9,16) have demonstrated decrements in short-term verbal memory during hypoglycemia. In the present study, the magnitude of the impairment induced by hypoglycemia was substantial, as indicated by the large effect size. However, the immediate Visual Reproduction Test was not significantly affected by hypoglycemia. This seemed to be a manifestation of a "ceiling effect" (i.e., most subjects obtained near-to-perfect scores), indicating a lack of sensitivity of this test to the stress of hypoglycemia.

A significant deterioration in performance on tests of delayed verbal memory has been shown during hypoglycemia in previous human studies of nondiabetic (6) and diabetic subjects (31). In the present study, all tests of delayed memory were markedly affected by hypoglycemia. Performance on the Delayed AVLT and Delayed Logical Memory Tests deteriorated significantly during hypoglycemia, and the effects of hypoglycemia on delayed visual memory were also considerable. Analysis of the immediate and delayed Logical Memory Test, AVLT, and the Visual Reproduction Test scores allowed calculation of the percentage of information that was learned and retained during the study. This revealed that, for tests of both verbal and visual memory, not only was less information recalled immediately after having studied the information during hypoglycemia as compared with euglycemia, but over time, subjects forgot more of what they had recalled immediately during hypoglycemia than during euglycemia.

Working memory was also very susceptible to the effects of hypoglycemia. The Working Digit Span Forward Test, the least difficult of the working memory tests, was least affected and was not significantly impaired during hypoglycemia. A small decrement was observed in the scores during hypoglycemia as compared with euglycemia, and the effect size was modest, indicating that although the effects of hypoglycemia on this test did not achieve significance in this study, hypoglycemia did impair test performance. The Working Digit Span Backward Test, the Letter/Number Sequencing Test, and the Validation Span Test were all more substantially impaired. The impact of hypoglycemia on performance in these tests was highly significant, and the extent of the decrements, as measured by the effect size, was large.

The adverse effects of hypoglycemia on impairment of memory in adults with type 1 diabetes that have been demonstrated in the present study are very similar to the effects of hypoglycemia on memory function in nondiabetic humans that we have shown previously (20). A previous study (9) has suggested that individuals with diabetes may be more susceptible to cognitive impairment during hypoglycemia. However, comparison of the results of the nondiabetic and diabetic groups showed no significant differences between the two groups. This may be attributable to the fact that the subjects with diabetes in our study were all young, had diabetes of short duration, and had normal hypoglycemia awareness. In addition, subjects in the diabetic and nondiabetic groups were matched for cognitive function. It is not known whether the effect of hypoglycemia on memory is sustained or protracted, and this will require further investigation. Many aspects of cognitive function have been observed to return to normal within 2 h after euglycemia is restored (32–34), and this is presumably similar for memory function.

Functional neuroimaging studies in humans (35,36) have confirmed that medial temporal lobe structures such as the hippocampus and adjacent parahippocampal regions are the principal structures involved with memory performance. The hippocampus is susceptible to a variety of toxic insults, including heavy metals (37), hypoxia (38), and drugs (39,40). There is some evidence that this particular area of the brain is also preferentially vulnerable to the adverse effects of hypoglycemia. Neuropathological observations have indicated that the brain is sensitive to neuroglycopenia in a rostrocaudal direction and that the cerebral cortex and hippocampus are most susceptible, whereas the brainstem and spinal cord are most resistant (41). Brains of human subjects who have suffered an episode of severe hypoglycemia have been studied (41,42) and were shown to have areas of cortical necrosis in the frontal lobes and hippocampus as well as relative sparing of the hindbrain. Anecdotal case reports of severe amnesia after an episode of severe hypoglycemia have identified a specific structural lesion in the hippocampus in individuals with insulin-treated diabetes (43,44).

The results of the present study have clearly demonstrated the short-term detrimental effects of acute hypoglycemia on memory and are consistent with these observations. However, the present study also demonstrated that other domains of cognition are impaired during moderately severe hypoglycemia, and there is now considerable evidence that acute neuroglycopenia causes rapid deterioration in psychomotor performance across a wide range of cognitive domains (3). It is feasible, therefore, that the impairment of memory performance observed in this study reflects a transient global brain dysfunction induced by hypoglycemia rather than specific vulnerability of memory processes to hypoglycemia. The very large effect size associated with the Validation Span Test, in particular, may be a consequence of task complexity. However, performance in another test of working memory was also very significantly impaired, to chance levels, in the same diabetic and nondiabetic subjects (45).

Individuals with insulin-treated diabetes are frequently exposed to varying degrees of hypoglycemia, and current therapeutic policies that strive to achieve strict glycemic control may promote more frequent hypoglycemic events. The re-

sults of the present study demonstrate that many individuals with type 1 diabetes are subject to substantial impairments of memory function during hypoglycemia in their everyday lives, which may have important practical implications for daily activities, including effective working ability and driving performance (46).

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