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Memory and insulin dependent diabetes mellitus (IDDM): Effects of childhood onset and severe hypoglycemia

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Abstract

Previous studies of the neuropsychological consequences of insulin dependent diabetes mellitus (IDDM) have had mixed and often contradictory results, possibly due to the heterogeneity of the samples and neuropsychological measures, and a lack of specific hypotheses. In order to address this problem, we focused on the effect of severe hypoglycemia on memory functioning in a relatively homogeneous sample of childhood-onset IDDM patients. Given the deleterious effects of hypoglycemia on medial temporal lobe structures (e.g., hippocampus) and the relationship between medial temporal damage and declarative memory functioning, we hypothesized that those patients who had experienced severe hypoglycemia would demonstrate impaired declarative memory and spared nondeclarative memory functioning. Results of the study were generally consistent with this hypothesis, although some impact of hypoglycemia was observed on perceptual priming ability. (*JINS*, 1997, *3*, 509–520.)

Keywords: Diabetes, Memory, Hypoglycemia

INTRODUCTION

Investigations of the effects of insulin dependent diabetes mellitus (IDDM) on memory, attention, and spatial and language functions have produced conflicting results. Some studies indicate that adults with IDDM exhibit few, if any, neuropsychological deficits (Ryan et al., 1984), whereas other studies document significant impairment, particularly in memory (Bale, 1973; Wredling et al., 1990) and higher cognitive functions such as abstraction (Franceschi et al., 1984). Investigators have suggested that two clinical factors related to IDDM, early age of onset and frequent, severe hypoglycemic episodes may discriminate between those patients with and without neuropsychological impairment (Holmes, 1990; Richardson, 1990; Ryan et al., 1988; Ryan, 1990). Although these factors have been studied extensively and shown to be associated with neuropsychological impairment, the nature of their joint effect on cognitive functioning has not been precisely explicated. The present study is an intermediate step towards this goal, as it considers the effect of hypoglycemia on patients within a restricted range of age of onset.

Of the two clinical variables described above, age of onset has been most consistently related to neuropsychological functioning in adults with IDDM. IDDM can be diagnosed at any age, but researchers generally have dichotomized patients into early-onset and late-onset groups (Ack et al., 1961). Early-onset patients perform more poorly than late-onset patients on tests of learning and memory, visuospatial functioning, and motor speed (Skenazy & Bigler, 1984; Ryan et al., 1985). The reasons for such effects are largely unknown. One possibility may be that, during development, the brain is more vulnerable to damage from metabolic insults that may accompany IDDM.

One such insult is hypoglycemia, which has been associated with the presence of neuropsychological deficits. Patients with IDDM who have experienced severe hypoglycemia generally perform more poorly on memory, visuospatial, and frontal lobe tasks than those who have not experienced severe hypoglycemia (Bale, 1973; Golden et al., 1989; Ryan,

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1990; Wredling et al., 1990), although a history of hypoglycemic episodes alone does not reliably predict the presence or type of deficits (Ryan, 1990). Some researchers attribute the correlation between hypoglycemia and neuropsychological deficits to permanent, diffuse neurological damage caused by this metabolic disturbance of the brain (Ryan et al., 1985). However, there is some evidence that certain areas of the brain are more vulnerable than others to damage from hypoglycemic insults, particularly the hippocampal region (Auer et al., 1984; 1989; Auer & Siejo, 1988; Chalmers et al., 1991). Cell death during hypoglycemia (and anoxia and ischemia) is thought to be caused in large part by an N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxic process (McCall, 1992). The susceptibility of the hippocampus to excitotoxicity is thought to be explained by the relatively high proportion of NMDA receptors in the hippocampal region (McCall, 1992). As the hippocampal region is closely associated with declarative memory functioning (Squire, 1992), this type of memory may be particularly sensitive to the effects of severe hypoglycemia (Richardson, 1990; Hershey et al., 1993). In support of this idea, case studies have associated severe hypoglycemia with specific deficits in delayed declarative memory (Chalmers et al., 1991; Hershey et al., 1993) and damage to the hippocampal region (Chalmers et al., 1991).

The idea that hypoglycemia causes diffuse cognitive deficits may be in part due to the fact that studies relating neuropsychological performance and hypoglycemic history have often used samples that are comprised of patients with highly variable ages of onset (Prescott et al., 1990; Wredling et al., 1990; Sachon et al., 1992) or patients with adult onset only (Langen et al., 1991). This method may obscure distinct patterns of deficits if age of onset interacts with the effects of hypoglycemia, or if there are neuropsychological deficits associated with different ages of onset, independent of the effects of hypoglycemia. Studies that have looked exclusively at one age-of-onset group or made comparisons across groups support this possibility (Ack et al., 1961; Gilhaus et al., 1973; Haumont et al., 1979; Ryan, 1990).

Severe or recurrent hypoglycemia may result in greater impairment in developing animals than in mature animals. Studies that have directly examined the effects of hypoglycemia on the developing brain are not prevalent. However, similar insults to the developing brain have resulted in increased neuronal damage (Kretschmann et al., 1986). In addition, hippocampal lesions early in development can produce more impairment on hippocampally mediated tasks than hippocampal lesions in adulthood (Douglas, 1975).

In summary, both the age of onset of IDDM, and the experience of severe hypoglycemia appear to have an impact on cognitive functioning. The present study focused on the neuropsychological performance of IDDM patients within a restricted range of age of onset (childhood) who either have or have not experienced severe hypoglycemic episodes. It was hypothesized that patients with childhood-onset IDDM and a history of severe hypoglycemic episodes would demonstrate more cognitive deficits than those who have not experienced severe hypoglycemia. Specifically, we hypothesized that the childhood-onset patients with a history of severe hypoglycemia would be particularly impaired on declarative memory tasks as compared to nondeclarative memory tasks and other cognitive skills.

METHODS

Research Participants

A normal comparison group (NC) consisted of 21 participants. The childhood-onset IDDM group consisted of 38 participants, all diagnosed before the age of 14. Twelve of the participants with IDDM had no severe hypoglycemia episodes (*childhood-onset, no hypoglycemia*) and 26 had 1 or more severe hypoglycemic episodes (*childhood-onset, hypoglycemia*). A severe hypoglycemic episode was defined as any situation in which medical attention was required for alleviation of hypoglycemic symptoms. This definition is similar to that used by the DCCT Research Group (1991) and other researchers (Ryan & Williams, 1993). This information was gained through a detailed interview. Due to the limited reliability of self-report data regarding the exact frequency and timing of hypoglycemic events experienced, we did not feel confident treating number of hypoglycemic episodes as a continuous variable, or dichotomizing patients in any other way besides absence or presence of a severe hypoglycemic episode (Ryan & Williams, 1993). The issue of when IDDM participants experienced severe hypoglycemia is an important one, which may have significant theoretical and practical consequences. This question, however, is best addressed in a prospective study rather than a retrospective design such as this present study. All IDDM participants had been diagnosed 5 or more years prior to their participation in this study and were members of a research volunteer group (Diabetes and Research Training Center Database, Washington University Medical School) whose diagnoses had been confirmed by medical personnel in charge of the group. All participants were between the ages of 15 and 42 years, were otherwise healthy, had no history of stroke or head injury, no significant retinopathy or neuropathy, and were not pregnant. Metabolic control was measured through reports of severe hypoglycemia, hyperglycemia, and glucose levels on the day of testing. See Table 1 for means and standard deviations of clinical and demographic variables.

Procedure

Participants were tested at the General Clinical Research Center at the Washington University Medical Center. All participants had a blood sample taken at the time of testing to determine their blood glucose level. Patients were tested only if they were not hypoglycemic (blood glucose < 80 mg/dl). All participants were given the same battery of tests beginning in the midafternoon. The battery, which took approximately 2.5 hr, consisted of tests designed to assess declarative and nondeclarative memory, frontal-related functions, and verbal and visuospatial skills.

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Table 1. Clinical and demographic variables

Variable	Normal Controls *M* (*SD*)	No hypoglycemia IDDM *M* (*SD*)	Hypoglycemia IDDM *M* (*SD*)
Age (years)	27.8 (8.1)	22.8 (7.7)	26.2 (6.6)
Education (years)	15.6 (1.6)	14.0 (3.3)	14.0 (3.2)
Shipley Vocabulary	33.5 (3.4)	30.5 (4.6)	27.0 (6.9)*
Age of onset	—	7.5 (4.3)	7.7 (3.4)
Number of hypoglycemic episodes	—	0.0 (0.0)	3.3 (3.7)
Number of hyperglycemic episodes	—	.42 (.67)	1.0 (1.5)

Asterisk denotes a significant difference from the normal control group, $p < .05$.
One hypoglycemic IDDM participant had 25 hyperglycemic episodes and was considered to be an outlier. There was no significant difference between groups either with or without that participant included. The number of hyperglycemic episodes shown above does not include this participant.

General cognitive measure

1. *Shipley Vocabulary Test*: This task was taken from the Shipley Institute of Living Scale (Shipley, 1946) as a measure of general verbal intelligence. Participants were given 30 words and asked to choose a synonym for each word from corresponding groups of 5 words. Total number of correct answers were recorded.

Declarative memory tasks

1. *Paragraph Recall Task*: This task was used to test verbal declarative memory, both immediate and delayed free recall. Participants heard two brief narratives, each containing 25 informational bits, and were asked to recall as much as possible immediately after hearing each paragraph, and following a 30-min delay. Credit was given for each informational bit recalled verbatim and half credit was given for accurate paraphrases. The paragraph recall task has been used extensively in previous investigations of the effects of glucose on memory (Craft et al., 1992; Newcomer et al., 1994) and is a well validated declarative memory task (Squire et al., 1987).
2. *California Verbal Learning Test (CVLT)*: This task (Delis et al., 1987) was used to test verbal declarative learning over several trials, and short and long term recall. Although this type of task is somewhat less sensitive to memory deficits than the Story Recall task (Lezak, 1979), it assesses the effects of repeated presentation as well as other variables. Poor performance on verbal recall measures has been associated with left medial temporal damage and dysfunction (Hermann et al., 1987, 1994). The participants were read a list of 16 nouns and asked to immediately recall as many items as possible from that list. The list was then read four more times, and the participants were asked to recall the list after each presentation. They then heard an entirely different second list, and were asked to recall this new list immediately. The participants were then asked to recall the first list (*free recall trial*), with no additional exposure to that list. A *cued recall trial* was also given. After a 20-min delay, the participants were asked to recall the first list (both free and cued recall trials) and to recognize items from a list of targets and distractors. In order to simplify analyses and to test the hypotheses most directly, only Trial 5 and Long Delay Recall variables were analyzed.
3. *Pattern Recall and Recognition Task*: These tasks were used to test visual declarative memory, both short and long recall and recognition. The stimuli for this task were three checkerboard patterns on a single sheet of paper. Each checkerboard was a large box subdivided into nine equal sections resulting in a 3×3 matrix. A given pattern consisted of four blackened sections in the matrix. Participants were told to study the three patterns for a total of 15 s. Immediately following this study period, the stimuli were removed from sight, and participants were asked to reproduce each pattern by blackening the appropriate squares on three blank checkerboards. Free recall of these patterns was tested after a 30-min delay. One point was given for each block that was correctly located. Immediately following delayed recall, participants were asked to pick the three test patterns from a display of 12 checkerboards that included 9 distractor patterns. For this condition, subjects were given 1 point for each pattern correctly recognized. Performance on recall trials of this task has shown to be related to glucose regulation in a previous study (Craft et al., 1992).

Nondeclarative memory tasks

1. *Picture Priming*: This task measures the effect of prior exposure to visual stimuli on a perceptual recognition task using degraded stimuli. The ability to recognize previously seen items more easily than novel items is called priming. Priming appears to be mediated by a different system than the medial temporal declarative memory system, and is thus not affected by amnesia (Gabrieli et al., 1994). Participants were shown 27 simple line drawings

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of common objects. They were asked to name each object and judge the objects for familiarity on a 5-point scale (from *very unfamiliar* to *very familiar*). The pictures were exposed for 4 s. Participants were not told to memorize or study the pictures. After all the pictures were presented, a 5-min distractor period occurred, during which participants performed the Serial Addition Task. Then participants were shown 18 sets of pictures. Each set consisted of four pictures of a given object. The last picture in the set was the intact object. The other three pictures were identical to the complete picture, except that they were degraded by having some percentage of the lines in the picture erased. The three degraded pictures had either approximately 25, 50, or 75% of the object erased. Half of the objects were pictures that had been presented in the study phase of the task, and the other half were objects that had not been presented earlier. In a previous study the two groups of objects were found to be equally identifiable (Craft et al., 1993). Three, 2, or 1 points were given if participants were able to identify the third, second or most degraded versions respectively. Participants received 4 points if they were only able to identify the object in its complete form. No one failed to identify an object by this stage. Scores were then averaged for the nine novel objects and the nine objects to which participants had prior exposure. Priming is demonstrated when the participants are, on average, able to name previously experienced pictures at an earlier stage than novel pictures.

2. *Word-Stem Priming*: Priming for verbal stimuli was measured with a word completion task (Squire et al., 1987). Again, this type of memory is not affected by damage to the medial temporal declarative memory system (Squire et al., 1987; Gabrieli et al., 1994). Participants were required to first simply pronounce a list of 15 words presented on a computer screen and judge each one on "familiarity" and "liking." A 5-point scale was used (from *very unfamiliar* or *dislike very much* to *very familiar* or *like very much*). The presentation rate was controlled at 4 s per word. Participants were not told to study or memorize the words. After two repetitions of the list, there was a 3-min distraction period, during which participants completed the Benton Judgment of Line Orientation (Benton et al., 1975). Then participants were shown a list of 20 three-letter word stems that had to be completed as quickly as possible to form a common English word (e.g., "STA" could be completed as "stand," "stare," etc.). Half of the stems could be completed to form one of the words from the original list (priming). The other half of the stems could be completed to form words not viewed previously in this task (baseline). All words were equivalent in frequency, and all stems could be completed with at least 10 common English words. One of the 10 possible word completions for each of these 20 stems was randomly chosen as the correct word completion. Half of these chosen words were used for priming and the other half were not presented. The frequency with which participants used the primed words to complete the matching stems was used as the *words primed* measure. The frequency with which participants used the unpresented words to complete the matching stems was used as the baseline measure. Both sets of words were equivalent in their priming and baseline effects (Squire et al., 1987). The difference between the two was taken as the priming effect. The examiner recorded participants' responses. Immediately following the word-stem completion task, participants were asked to recall as many of the words that they had seen on the computer screen and had rated for familiarity and liking (total = 15). This task was added in order to measure declarative recall for the words presented.

3. *Serial Reaction Time Task*: This task measures implicit motor memory, and was originally described by Nissen et al. (1989). Participants sat in front of a computer screen with their middle and index fingers placed on four evenly spaced keys corresponding to four evenly spaced locations across the computer screen. They were instructed to simply press the key that corresponds to the location of an asterisk that appeared on the screen. Once a key was pressed, another asterisk appeared in another location, and participants had to press that corresponding key as fast as they could, and so on. The trials were divided into six blocks of 100 trials each. Trials in blocks 1, 2, and 6 were randomly generated by the computer; there was no pattern to the appearance of the asterisk. However, trials in Blocks 3, 4, and 5 followed a pattern of 10 asterisk locations. That pattern was repeated 10 times in each block for a total of 20 repetitions of the same 10-location pattern. Reaction time was recorded for each trial, measured as the time between onset of the asterisk and the keypress. Performance improves (reaction time decreases) across the three patterned blocks. This improvement demonstrates motor learning and is dissociable from declarative, explicit knowledge of the pattern (Nissen et al., 1989). In the final random block, reaction times increase to approximately match performance in Blocks 1 and 2.

4. *Tactile Mazes*: This task measures motor and spatial memory in the absence of visual guidance. Performance is thought to be mediated by both declarative and nondeclarative memory systems (Nissen et al., 1989). Improvements in the maze completion time across trials is thought to be a reflection of strengthening nondeclarative memory (learning to execute the strategy for escaping deadends), and a decrease in errors across trials is a reflection of declarative memory (explicit knowledge of the correct route; Nissen et al., 1989). The stimulus was a large (76 $\times$ 46 cm), thin (1.25 cm) piece of wood with a T-maze cut through it. The maze had 10 choice points, each with an equal length dead end. A piece of blank paper was placed underneath the maze to record the response pattern. The participants were blindfolded, given a pencil and directed to the start box. They were then instructed to work their

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way through the maze as quickly and as accurately as possible. This procedure was carried out five consecutive times. Time taken to get through the maze on each trial, number of dead ends entered, and number of perseverative responses were recorded by the examiner.

Tasks sensitive to frontal lobe dysfunction

1. *Serial Addition Test*: This task was similar to the Paced Auditory Serial Addition Task, which assesses simple attention and mental control (Gronell & Wrightson, 1981; O'Donnel et al., 1994). Participants listened to a taped presentation of a string of 11 digits and asked to produce the sum of these numbers. Six strings were given, two trials at three different rates of presentation (2-, 1.5- and 1-s intervals between the digits). Errors were recorded.
2. *Auditory Trails–Continuous Performance Task*: This task primarily assesses sustained attention (Weintraub & Mesulam, 1985). Participants listened to a taped presentation of a string of randomly arranged letters and asked to identify the letters of the alphabet in order as they appear in the random string. Letters were presented at 1-s intervals. Omission, false positives and late signals were recorded as errors.
3. *Verbal Fluency Test (Milner, 1964; Benton, 1968)*: Participants were given a letter and asked to generate as many words as possible that started with that letter in 60 s. Three trials were given, each with a different letter (F, A, and S). Participants were instructed not to include proper nouns, repeated versions of a word (e.g.., "early," "earlier"), and number names. One point was given for each valid response.
4. *Stroop Color-Word Interference Task (Perret, 1974)*: This task is sensitive to prefrontal cortex damage and is thought to assess inhibition of prepotent responses (Larrue et al., 1994; Vendrell et al., 1995). Participants were given three conditions. In the first condition (word reading), a page with columns of color-words typed in black ink (blue, green, or red) was placed in front of the participants. They were instructed to read the columns as quickly as possible. In the second condition, participants were shown a page of blocks of colors, again arranged in columns. They were instructed to name the color of the blocks (blue, green, or red) as quickly and as accurately as possible. In the third condition, participants were shown a page of color-words typed in colored ink (blue, green, or red). The words were typed in conflicting colors (e.g., the word "RED" typed in blue ink). Participants were instructed to name the color of the ink for each word. Total time to complete each condition and number of errors committed were recorded.

Visuospatial tasks

1. *Benton Judgment of Line Orientation Task (Benton, et al., 1975)*: This task is a nonmemory task of simple visuospatial perception. Participants were presented with a template of 11 radiating lines of differing orientations. Each line was numbered. Test items, consisting of two unnumbered lines of different orientations, appeared below the template. Participants were asked to match 5 practice items and 30 test items to the corresponding lines on the template by indicating the appropriate numbers. One point was given for each correctly identified line.
2. *Woodcock-Johnson Spatial Relations Subtest*: This task measures complex visuospatial processing (Woodcock & Johnson, 1990). Participants were shown a complete shape and a selection of smaller pieces. They were instructed to choose the pieces that could be fitted together to form the complete shape. Four practice and 33 test trials were given. Number of correct test trials was recorded.

RESULTS

Demographic and Clinical Variables

Mean age at time of testing and mean years of education were statistically equivalent across all three groups. Mean age of diagnosis was also similar between the two IDDM groups. See Table 1 for means and standard deviations of clinical and demographic variables.

General Cognitive Measure

1. Shipley Vocabulary Test: A general linear models analysis was conducted on Shipley Vocabulary scores (total number of items correct) with group (normal control, no hypoglycemia IDDM, hypoglycemia IDDM) as the independent variable. A significant effect of Group × Performance [$F(2,54) = 8.17$, $p < .01$] was obtained. *Post-hoc* Student Newman-Keuls comparisons revealed that the hypoglycemia group scored significantly lower than the normal control group (see Table 1).

Declarative Memory Tasks

1. Story Recall Task: A repeated-measures ANOVA was conducted on Story Recall scores, with delay (immediate and delayed recall trials) as the repeated measure and group membership as the independent variable. This analysis revealed a significant effect of group [$F(2,56) = 3.76$, $p < .05$], condition [immediate *vs*. delayed recall; $F(1,56) = 38.25$, $p < .01$], and a significant interaction of Group × Condition [$F(2,56) = 4.41$, $p < .05$]. In order to determine which groups were most responsible for this interaction, repeated measures ANOVAs were conducted on pairs of groups. These ANOVAs revealed that the interaction was primarily between the normal control group and the hypoglycemia IDDM group [$F(1,45) = 6.78$, $p < .05$]. The interaction was not significant when comparing nor-

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mal controls to the no-hypoglycemia IDDM group or when comparing the two IDDM groups. Finally, on the delayed recall trial, *post-hoc* comparisons (Student Newman-Keuls) revealed that the hypoglycemia IDDM group performed significantly worse than either the normal controls or the no-hypoglycemia IDDM group (see Figure 1).

2. CVLT: Similar results were obtained with the CVLT. A repeated measures ANOVA was conducted on Trial 5 Recall (immediate recall) and Long Delay Recall (delayed recall) scores with delay as the repeated measure and group as the independent measure. Significant effects of group [$F(2,56) = 7.87$, $p < .01$] and delay [$F(1,56) = 36.36$, $p < .01$] were obtained, as well as a significant interaction of Group × Delay [$F(2,56) = 4.10$, $p < .05$]. In order to determine which groups were responsible for this interaction, repeated measures ANOVAs were conducted on pairs of groups. These analyses revealed that the interaction was primarily between the normal controls and the hypoglycemia IDDM group [$F(1,45) = 8.82$, $p < .01$]. The interaction was not significant in the other two ANOVAs (normal controls *vs*. the no-hypoglycemia group, no-hypoglycemia group *vs*. hypoglycemia group). In addition, *post-hoc* comparisons demonstrated that the hypoglycemia IDDM group performed significantly worse than the normal controls at both immediate and delayed recall (see Figure 2).

3. Pattern Recall and Recognition Task: A repeated measures ANOVA was conducted on immediate recall and delayed recall scores from the Pattern Recall Task. Delay was the repeated measure and group was the independent measure. No significant main effects or interactions were obtained. A one-way ANOVA was also conducted on recognition scores, with group as the independent variable. The main effect of group was not significant (see Table 2).

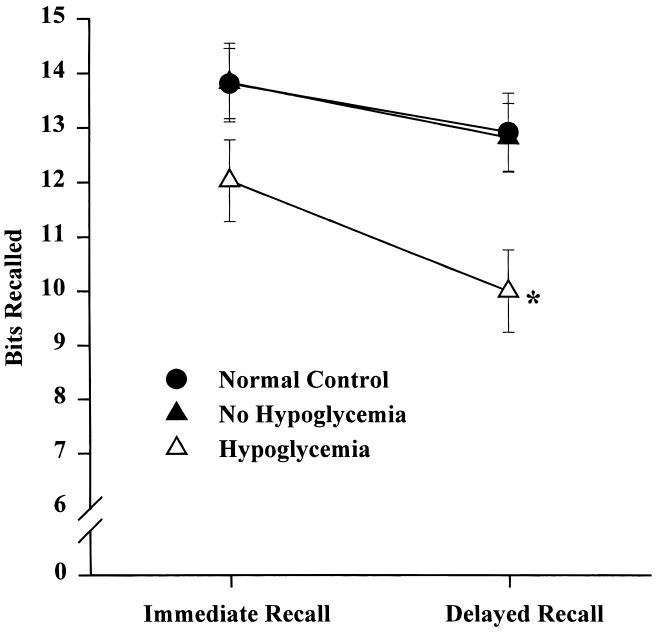

Fig. 1. Story recall; mean bits recalled and standard errors for each group at immediate and delayed recall trials. Asterisk denotes a significant difference from the normal control group *and* the no-hypoglycemia IDDM group, $p < .05$.

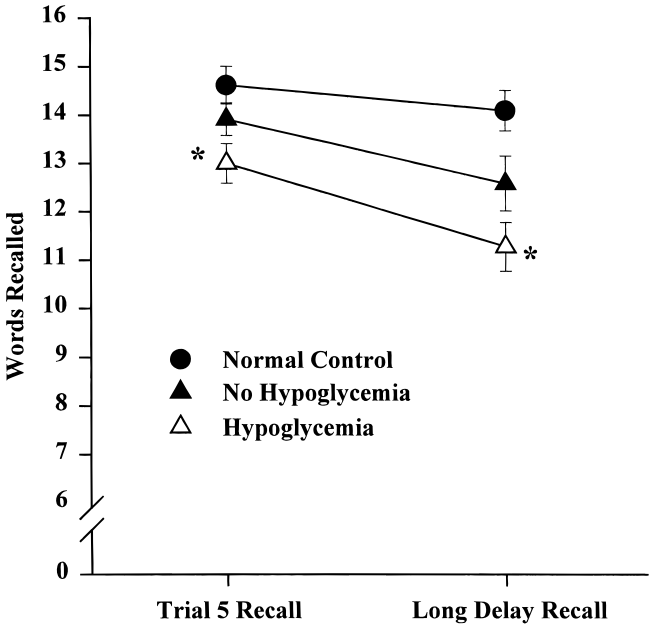

Fig. 2. CVLT; mean words recalled and standard errors for each group at Trial 5 and Long Delay recall trials. Asterisk denotes a significant difference from the normal control group, $p < .05$.

Nondeclarative Memory Tasks

1. Picture Priming: A one-way ANOVA was conducted on the average identification scores for the unprimed pictures (baseline measure). A significant effect of group was obtained [$F(2,56) = 6.23$, $p < .01$]. *Post-hoc* Student Newman-Keuls comparisons revealed that both IDDM groups performed significantly worse than the normal control group (see Table 2). In addition, a one-way ANOVA was conducted on the average identification scores for the primed pictures. A significant effect of group was obtained [$F(2,56) = 6.55$, $p < .01$]. *Post-hoc* Student Newman-Keuls comparisons revealed that the hypoglycemia IDDM group performed worse than the normal control group (see Table 2). However, following Snodgrass' (1989) statistical approach to correct for differences in baseline performance, a proportional score was calculated using the following formula: (identification score of primed items − identification score for unprimed items) / (1 − identification score of primed items). This formula generated a *relative priming effect*, which was analyzed with a one-way ANOVA. No differences between groups were found on this measure ($p = .68$).

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Table 2. Task variables by group

Task variable	Normal controls *M* (*SD*)	No-hypoglycemia IDDM *M* (*SD*)	Hypoglycemia IDDM *M* (*SD*)
Declarative memory tasks			
Pattern Recall			
Immediate Recall	10.7 (2.2)	9.9 (2.6)	9.7 (2.4)
Delayed Recall	10.8 (1.8)	9.3 (2.8)	9.7 (2.5)
Recognition	2.9 (0.5)	2.8 (0.6)	2.7 (0.6)
Nondeclarative memory tasks			
Picture Priming			
Primed	2.2 (0.4)	2.5 (0.4)*	2.6 (0.3)*
Unprimed	2.4 (0.3)	2.6 (0.3)	2.7 (0.3)*
Priming effect	0.15 (0.39)	0.17 (0.34)	0.07 (0.41)
Word-Stem Priming			
Words primed	4.4 (2.0)	2.8 (1.2)*	3.6 (1.6)
Baseline	1.1 (0.9)	0.4 (0.5)*	1.0 (0.7)
Priming effect	3.4 (1.9)	2.5 (1.4)	2.6 (1.5)
Serial Reaction Time Task, mean reaction time (ms)			
Random, Block 1	529 (98)	604 (202)	620 (153)
Patterned, Block 2	481 (113)	572 (220)	588 (144)
Patterned, Block 3	462 (95)	557 (248)	559 (133)
Patterned, Block 4	443 (99)	513 (242)	537 (137)
Random, Block 5	515 (89)	578 (225)	604 (142)
Serial Reaction Time Task, mean accuracy			
Random, Block1	.95 (.07)	.98 (.01)	.92 (.16)
Patterned, Block 2	.97 (.05)	.99 (.02)	.93 (.14)
Patterned, Block 3	.97 (.04)	.99 (.02)	.93 (.16)
Patterned, Block 4	.97 (.04)	.98 (.02)	.93 (.15)
Random, Block 5	.95 (.06)	.98 (.01)	.92 (.16)
Tactile Maze, mean time (s)			
Trial 1	66.6 (23.9)	59.8 (32.0)	69.9 (49.3)
Trial 2	46.2 (15.0)	32.8 (15.2)	45.3 (28.6)
Trial 3	37.8 (16.0)	27.8 (11.4)	35.5 (19.3)
Trial 4	21.5 (11.6)	23.2 (9.2)	31.3 (15.4)
Trial 5	27.3 (9.8)	20.3 (7.6)	31.1 (17.2)
Tactile Maze, mean errors			
Trial 1	3.4 (1.1)	3.8 (1.3)	4.2 (1.5)
Trial 2	3.3 (0.8)	3.2 (1.4)	3.8 (2.0)
Trial 3	3.1 (1.4)	3.5 (1.2)	3.4 (1.4)
Trial 4	3.4 (1.2)	2.8 (1.3)	3.0 (1.5)
Trial 5	3.3 (1.5)	2.6 (1.1)	3.8 (1.6)
Tasks sensitive to frontal lobe dysfunction			
Serial Addition, errors	1.3 (1.6)	1.3 (1.2)	1.0 (1.5)
Auditory A's, errors	.19 (.51)	.42 (.67)	.20 (.50)
Verbal Fluency, words generated	47.1 (7.6)	37.3 (8.0)*	36.3 (8.7)*
Stroop, mean errors			
Word	.52 (.68)	.18 (.40)	.88 (1.6)
Color	1.4 (1.8)	1.9 (2.7)	2.0 (1.8)
Interference	2.8 (2.9)	4.4 (6.4)	4.7 (5.5)
Stroop, mean time to complete (s)			
Word	42.9 (7.5)	39.8 (5.3)	48.4 (9.6)
Color	53.8 (8.9)	55.0 (9.5)	64.4 (18.7)
Interference	92.8 (18.8)	96.6 (20.5)	112.3 (43.3)
Visuospatial tasks			
Benton Line Orientation, number correct	24.7 (3.7)	25.8 (2.9)	24.7 (4.0)
Spatial Relations, number correct	26.0 (4.0)	24.9 (2.6)	24.8 (4.5)

Note. $*$ = significant difference from normal control group, $p < .05$.

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Priming effects were also examined by comparing baseline and priming performance scores with 1-tailed paired *t* tests for each group (Corwin & Snodgrass, 1987). Significant differences were found for the normal control group ($p < .05$), trend level effects were found for the no-hypoglycemia IDDM group ($p = .06$), and no effect was found for the hypoglycemia group ($p > .1$).

In summary, both IDDM groups had more difficulty identifying unprimed pictures relative to controls, whereas only the hypoglycemia IDDM group had difficulty identifying primed pictures relative to controls. Although both IDDM groups demonstrated statistically equivalent levels of relative priming compared to normal controls, the hypoglycemia group did not demonstrate a priming effect when examined alone. These findings indicate that patients with IDDM, particularly those with hypoglycemia, may have some difficulty accurately perceiving degraded stimuli. In addition, the hypoglycemia IDDM group may have impaired perceptual priming.

2. Word-Stem Priming Task: A one-way ANOVA was conducted on the total number of word stems completed with words from the unpresented list (baseline measure). A nearly significant effect of group was obtained [$F(2,54) = 3.12$, $p = .052$]. *Post-hoc* Student Newman-Keuls comparisons revealed that the no-hypoglycemia IDDM group completed fewer word stems with unpresented words (lower baseline performance) than the normal control group (see Table 2). In addition, a one-way ANOVA was conducted on the total number of words successfully primed with group as the independent variable. A significant effect of group was obtained [$F(2,54) = 3.36$, $p < .05$]. *Post-hoc* Student Newman-Keuls comparisons revealed that the no-hypoglycemia IDDM group performed worse than the normal control group (see Table 2). Following Squire et al. (1987), baseline performance was subtracted from priming performance and analyzed. No differences were found between groups on this corrected priming measure, indicating that the relative size of the priming effect was similar across groups. Paired *t* tests were then conducted for baseline and priming performance within each group. Significant differences ($p < .01$) were found for each group. Thus, the no-hypoglycemia IDDM group appeared to have difficulty with some of the fundamental skills necessary for this task, such as rapidly retrieving words to meet particular requirements, but did demonstrate the normal priming effects. Notably, the hypoglycemia IDDM group did not differ from the control group on baseline, priming, or corrected priming measures.

   Another one-way ANOVA was conducted on the total number of words recalled at the end of the word-stem priming task. A significant effect of group was found [$F(2,54) = 5.25$, $p < .01$]. *Post-hoc* comparisons revealed that the hypoglycemia IDDM group recalled significantly fewer words than the normal control group (see Figure 3).

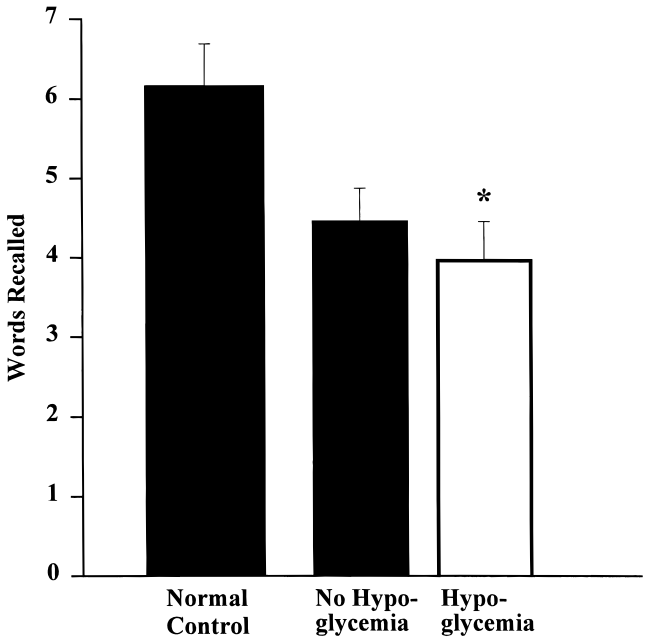

Fig. 3. Word-Stem Priming; mean number of words recalled and standard errors for each group. Asterisk denotes a significant difference from the normal control group, $p < .05$.

3. Serial Reaction Time Task: Repeated measures ANOVAs were conducted on both reaction time and accuracy with condition as the repeated measure and group as the independent variable. The main effect of condition was significant for both reaction time [$F(4,52) = 68.6$, $p < .01$] and accuracy [$F(4,52) = 5.6$, $p < .01$]. Neither ANOVA revealed any significant interactions or main effects of group (see Table 2).

4. Tactile Maze Task: Repeated measures ANOVAs were conducted on both time to complete and errors with trial (1–5) as the repeated measure and group as the independent variable. The main effect of condition was significant for both completion time [$F(4,50) = 43.21$, $p < .01$] and errors [$F(4,54) = 2.78$, $p < .05$]. Neither ANOVA revealed any significant interactions or main effects of group (see Table 2).

Tasks Sensitive to Frontal Lobe Dysfunction

1. Serial Addition Task: A one-way ANOVA was conducted on total number of errors with group as the independent variable. The effect of group was not significant (see Table 2).

2. Auditory Trails: A one-way ANOVA was conducted on total number of errors with group as the independent variable. The effect of group was not significant (see Table 2).

3. Verbal Fluency Task: A one-way ANOVA was conducted on the total number of correctly generated words, with group as the independent variable. A significant ef-

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fect of group was obtained [$F(2,56) = 11.14$, $p < .01$). *Post-hoc* Student Newman-Keuls comparisons revealed that both IDDM groups performed worse on this task as compared to the normal control group (see Table 2).

4. Stroop Color-Word Interference Test: Separate repeated measures ANOVAs were conducted on Stroop error scores and total time to complete each condition. For each analysis, condition was the repeated measures (word, color, word–color) and group was the independent variable. The analysis of errors did not reveal any significant effects or interactions except for a main effect for condition [$F(2,54) = 22.62$, $p < .01$]. The analysis of total time (averaged across conditions) revealed a significant effect of condition [$F(2,54) = 171.46$, $p < .01$] and group [$F(2,55) = 3.62$, $p < .05$]. *Post-hoc* comparisons demonstrated that the hypoglycemia IDDM group performed significantly slower overall than the normal control group (see Table 2).

Visuospatial Tasks

1. Benton Line Orientation: A one-way ANOVA was conducted on total number of correct answers with group as the independent variable. The effect of group was not significant (see Table 2).
2. Woodcock-Johnson Spatial Relations Subtest: A one-way ANOVA was conducted on total number of correct answers with group as the independent variable. The effect of group was not significant (see Table 2).

Summary of Results

In summary, these analyses demonstrated that the group of IDDM patients who had experienced severe hypoglycemia had distinct deficits, primarily in the delayed recall of verbal information (Story Recall, CVLT, Word-Stem Recall). This group also performed more poorly on a test of vocabulary (Shipley Vocabulary Test) and was slower overall to complete the Stroop Color-Word Interference Task. The no-hypoglycemia group performed worse than normal controls on rapid word-stem completion (Word Stem), but all groups demonstrated a significant effect of priming. Both IDDM groups (with and without severe hypoglycemia) in general performed worse than normal controls on Verbal Fluency, and on a task requiring the identification of degraded pictures (Picture Priming). However, in addition, the hypoglycemia IDDM group did not demonstrate priming on the Picture Priming task. No between group differences were found on nondeclarative motor tasks or on tests of attention or visuospatial functioning.

DISCUSSION

This study was designed to separate the general effects of childhood-onset IDDM from the hypothesized specific effects of severe hypoglycemia on neuropsychological performance. It was predicted that participants with IDDM who had a history of severe hypoglycemia would demonstrate significantly impaired delayed declarative memory, yet be relatively unimpaired on nondeclarative memory tasks. This hypothesis was generally supported by the present data. In addition, it was found that childhood-onset IDDM was associated with impairment on specific tasks independent of hypoglycemic experience.

In patients with childhood-onset IDDM, a history of severe hypoglycemia correlated with deficits in delayed recall for verbal information. In three different measures of verbal recall (Story Recall, CVLT, Word-Stem Recall Task), the group who had experienced severe hypoglycemic episodes performed significantly worse on delayed recall trials, indicating difficulty with recalling new information after a delay. This effect was most striking on the Story Recall task, where the no-hypoglycemia IDDM group performed as well as the normal control group, and the hypoglycemia IDDM group performed much worse than either group (approximately 33% less information recalled than normal controls, 22% less than no-hypoglycemia group). On the CVLT and Word-Stem Recall Task, both IDDM groups performed more poorly than the normal controls, but only the hypoglycemia group was significantly worse than the normal controls (CVLT: approximately 21% fewer words recalled than normal controls, 11% fewer than no-hypoglycemia group; Word-Stem: approximately 36% fewer words recalled than normal controls; 12% fewer than no-hypoglycemia group). Notably, no deficits were observed on procedural nondeclarative tasks (Tactile Maze, Serial Reaction Time) or on the Word-Stem Priming task, indicating that the medial temporal declarative memory system was primarily disturbed by the experience of severe hypoglycemia. However, the hypoglycemia group did not demonstrate a priming effect on the Picture Priming task. This result may be due to the possibility that declarative memory can enhance priming performance, particularly when there are are only a small number of easily rehearsed stimuli used, such as in this task (Haist et al., 1991). If performance on this task is influenced by declarative memory skills, it would follow that the hypoglycemia group would perform more poorly than the no-hypoglycemia group or the control group. The status of visual priming in these groups is therefore uncertain and would best be directly addressed with a more challenging picture priming task.

These findings suggest that for patients with childhood-onset IDDM, severe hypoglycemia can have significant consequences for neuropsychological functioning that are independent of generalized disease effects. The effects on memory functioning are particularly pronounced, and are conceivably large enough to have a detectable impact on aspects of daily functioning, such as school performance. It remains to be explored whether the combined effect of an early age of onset and the experience of severe hypoglycemia may be particularly harmful to the proper development or acquisition of declarative memory functioning. In order

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to test this hypothesis, the memory performance of adult-onset IDDM patients with and without a history of severe hypoglycemia would have to be examined. A more ambitious study would be to follow patients with IDDM from onset to adulthood, measuring each hypoglycemic episode across development and adulthood.

A second pattern of results indicates that childhood-onset IDDM, regardless of hypoglycemic history, is associated with the presence of deficits on two very different tests; the Verbal Fluency test, and visual completion (Picture Priming). Verbal fluency has been related to prefrontal functioning, particularly left prefrontal cortex (Milner, 1975). The Picture Priming task involves identifying primed and unprimed objects in degraded form, a skill that is impaired in apperceptive agnosia. Patients with apperceptive agnosia often have damage to the right temporal cortex (Milner, 1958; Kolb & Whishaw, 1990) or right parietal, particularly inferior parietal, cortex (Warrington & James, 1967; McCarthy & Warrington, 1990). Performance on both of these tasks appear to be vulnerable to some aspect of childhood-onset IDDM that is independent of hypoglycemic experience. Early-onset IDDM has been proposed to affect many skills due to interference with school attendance and attentiveness (Ryan, 1990), but may also affect neurological development in unknown ways.

In addition, the hypoglycemia IDDM group performed more poorly on the Shipley Vocabulary Test than the normal control group, but was not significantly different from the no-hypoglycemia group. One possible explanation for this difference could be that poor declarative memory interferes with either vocabulary acquisition (Verfaellie et al., 1995) or retrieval of previously learned information. An alternative possibility is that poor vocabulary can affect performance on verbal memory tasks. However, the words used in the Story Recall, CVLT, and Word Priming Recall tasks were relatively simple and concrete compared to the Shipley Vocabulary words. Further, within the normal controls, Shipley performance was significantly correlated with delayed Story Recall ($r = .52$, $p < .05$) but not with any other declarative memory tests, making it an unlikely explanation for declarative memory performance across all tasks.

A third finding from this study is that general visuospatial functioning aside from picture identification (Benton Line Orientation, Woodcock-Johnson Spatial Relations) and sustained attentional skills (Auditory A's, Serial Addition) were not affected by childhood-onset IDDM, either with or without a history of severe hypoglycemia. However, a history of severe hypoglycemia did affect overall speed on the Stroop task. These results argue against the presence of generalized cognitive deficits associated with either childhood-onset IDDM or severe hypoglycemia.

There are several limitations to the explanatory power of this study, most of which involve the difficulty of measuring hypoglycemic episodes. In a retrospective study the frequency, severity, and timing of hypoglycemic episodes cannot be controlled and can only be estimated. This methodology is thus unreliable for the finer analysis of these variables. In order to accurately address the impact of these variables on neuropsychological functioning, a prospective design would have to be implemented, or animal models used. We would expect that greater severity and higher frequency of hypoglycemic episodes would be related to an increased risk of detectable memory deficits. In addition, we would expect that hypoglycemia may be more likely to damage the brain and interfere with cognitive functioning (and development) during early childhood. The present study, however, is limited in its ability to precisely relate hypoglycemic variables to neuropsychological functioning. However, this study does serve to clearly associate a history of severe hypoglycemia with significant risk for declarative memory deficits.

In conclusion, by matching IDDM groups on age of onset within a restricted range, we were able to more accurately measure the effects of severe hypoglycemia on neuropsychological functioning, particularly within the domain of memory. In the context of childhood-onset IDDM, the results of this study support the hypothesis that severe hypoglycemia has a specific, rather than diffuse, effect on neuropsychological functioning: It most prominently affects the ability to recall newly learned information following a delay. The system believed to support this ability, the medial temporal declarative memory system, relies heavily on the hippocampal region, a region that is particularly affected by the harmful metabolic state of severe hypoglycemia. Our findings suggest that severe hypoglycemia poses a significant threat to medial temporal function. One possible clinical implication of this finding is that great care should be taken not to impose overly strict standards for control in young patients with IDDM, due to the increased risk of hypoglycemia associated with such regimens (The DCCT Research Group, 1991). This caveat is particularly relevant given recent proposals from the Diabetes Control and Complications Trial that strict control is desirable for adults with IDDM (The DCCT Research Group, 1993). Such recommendations may not be valid for younger patients (Rapaport & Sills, 1994) and may in fact increase the risk for memory impairment in this group.

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