

Original Article

A prospective study of severe hypoglycemia and long-term spatial memory in children with type 1 diabetes

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Abstract: In a previous retrospective study, severe hypoglycemia (SH) was associated with decreased long-term spatial memory in children with type 1 diabetes mellitus (T1DM). In this study, we tested the hypothesis that prospectively ascertained SH would also be associated with decreased spatial long-term memory over time. Children with T1DM ($n = 42$) and sibling controls ($n = 25$) performed a spatial delayed response (SDR) task with short and long delays and other neuropsychological tests at baseline and after 15 months of monitoring. Extreme glycemic events and other medical complications were recorded prospectively during follow-up. Fourteen T1DM children experienced at least one episode of SH during the follow-up period (range = 1–5). After controlling for long-delay SDR performance at baseline, age, gender, and age of onset, the presence of SH during the prospective period was statistically associated with decreased long-delay SDR performance at follow-up (semipartial $r = -0.38$, $p = 0.017$). This relationship was not seen with short-delay SDR or with verbal or object memory, attention, or motor speed. These results, together with previously reported data, support the hypothesis that SH has specific, negative effects on spatial memory skills in T1DM children.

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Severe hypoglycemia (SH), a significant complication of insulin treatment for type 1 diabetes mellitus (T1DM), is more common during childhood than adulthood (1). Thus, individuals with childhood onset T1DM may experience disease effects and complications including SH during periods of neural and cognitive development. Although profound hypoglycemia can cause coma and death (2), the vast majority of SH episodes are not as acutely significant. However, they could still pose some risk to brain function, even after glucose levels have been stabilized. Understanding the effects of SH on the developing brain is critical in the selection of optimal treatment strategies, especially during childhood.

Animal and human neuropathological data suggest that SH preferentially affects the hippocampus and medial temporal region of the brain (3–6). Based on this pattern, we hypothesized that tasks sensitive to dysfunction of these regions, such as delayed response tasks, would be most sensitive to the effects of SH. Delayed response tasks are well-validated memory tasks that require subjects to remember information over varying delays. Short delays require short-term memory and intact dorsolateral prefrontal function (7–11), whereas long delays are thought to rely upon long-term memory and the medial temporal region (12–20).

Our previous work has suggested that SH has a preferential impact on spatial long-term memory in children (21–23). Case studies have also associated profound hypoglycemia with specific deficits in long-term memory (6, 24, 25). Some studies using clinical neuropsychological tools have reported findings consistent with an effect of SH on memory function (26–28), whereas others have argued that SH has a diffuse or even no impact on cognition and the brain in children (29, 30), adolescents, and adults (31, 32).

Thus, the precise effects of SH on cognition in children remain controversial. Our previous study was retrospective in nature and so limited by the absence of baseline measures of cognitive performance (22). To test more conservatively the hypothesis that SH has a negative impact on long-delay spatial delayed response (SDR) performance, we tested children with T1DM with SDR and other measures at entry to the study and after 15 months of monitoring. Change in performance was then related to the presence of SH that occurred during the monitoring period.

Research design and methods

Participants

Children with T1DM were recruited from a larger treatment study ($n=69$) conducted at Washington University School of Medicine and St. Louis Children's Hospital. The treatment study enrolled patients between 6 and 16 yr old who had T1DM for at least 2 yr or were diagnosed for at least 1 yr and had negligible stimulated C-peptide, confirming T1DM. Patients were excluded for chronic diseases other than well-controlled asthma or Hashimoto's thyroiditis, or evidence of diabetic retinopathy, nephropathy or neuropathy, mental retardation, special education enrollment, major mental illnesses, significant neurological history not due to diabetes (e.g., head injury with loss of consciousness), or for parental illiteracy, non-fluency in English, depression, psychosis, or substance abuse. Siblings of these patients who met the above criteria but were not diagnosed with T1DM were also recruited to serve as a control group for the current study. Both the larger treatment study and the current study were approved by the Human Studies Committee at Washington University School of Medicine and were performed in accordance with the Declaration of Helsinki.

At the beginning of the treatment study, children were randomly assigned to either an intensive therapy (IT) or usual care (UC) treatment regimen. Children were recruited and enrolled in the current study around the time of randomization. Children were tested at enrollment (baseline) and then again at the end of their participation in the 18-month treatment study (follow-up). Analyses relating baseline performance to SH occurring before entry to the study have been published previously (22).

Procedures

Glycemic events.

Each child's history of SH and hyperglycemic events that occurred prior to baseline was determined through a detailed interview with one or both of the child's parents by a single examiner (RL) (22). Parents were also asked to report SH events on an ongoing basis during the follow-up period. A nurse or physician interviewed parents after each SH episode, recording the symptoms experienced, circumstances of the event, treatment given, and any glucose levels obtained. In addition, these events and any additional events were reviewed at each child's monthly or quarterly visits. A hypoglycemic episode was coded as severe, if the episode was associated with neurological dysfunction such as seizure, loss of consciousness, or inability to arouse from sleep, or assistance of someone other than the patient was required for treatment (33). Treatment could be given in the form of food or drink, a glucagon injection, or intravenous glucose. Severe hyperglycemia was defined as blood glucose readings >500 mg/dL and ketoacidosis.

Blood glucose levels.

Blood glucose levels were determined in T1DM subjects prior to each testing session. If subjects were hypoglycemic (<60 mg/dL), a snack or lunch was given in consultation with the study nurse (MS). Blood glucose levels were measured again after approximately 30 min, and cognitive testing began only when euglycemia was established.

Cognitive testing

Spatial memory.

SDR: This task was used to measure spatial memory across short and long delays (19, 20, 23). Subjects must remember the location of a dot on a computer screen. Participants were seated approximately 60 cm from the monitor and had to focus on a cross in the center of the screen. A black dot (10 mm diameter) was presented for 150 ms in one of 32 possible locations at a radius of 950 mm from the center of the screen. Next, a delay of either 5 or 60 s was imposed. During the delay, subjects performed a continuous performance task designed to keep their eyes focused on the center of the screen. This task presented shapes (squares, triangles, or diamonds) in random order (stimulus duration = 1000 ms, intertrial interval = 750 ms) in the center of the screen. Participants were instructed to press the space bar every time they saw a diamond shape appear. At the end of the delay, the cross reappeared and subjects were told to point to the location on the screen where they remembered seeing the dot. The x and y position of their finger was recorded by placing a mouse cursor under their fingertip.

This position was then automatically compared to the location of the original dot and error in mm was calculated. Twenty-four trials were presented in random order, with eight trials in each condition: 5 s short delay, 60 s long delay, or cue present. In the cue-present trials, the dot remained on the screen during recall and participants were asked to put their finger on the dot; this allowed for an assessment of pointing and measurement error.

Verbal memory.

Paragraph recall: This task was based on a standard story-recall task and is a well-validated measure of verbal declarative memory for narrative information (34–36). Participants listened to a brief taped narrative passage consisting of 44 bits of information. Participants were then asked to provide verbatim recall immediately and after a 90-min delay. Responses were recorded verbatim and scored. Subjects were given full credit for bits recalled exactly as presented and half credit for acceptable paraphrases (37). The percent of material retained across the delay was calculated.

California verbal learning task – children’s version (CVLT-C): This task assessed verbal learning (38). Participants are read a list of 15 words (List A) and asked to recall the words for five consecutive trials. They are then read a second list (List B) and asked to recall this new list. They then must recall List A words in both a free recall trial and a category-cued trial. An additional free recall trial and category-cued trial are administered after a 20-min delay along with a recognition task.

Object memory.

Delayed match to sample, list presentation (DMSL): This task assesses visual recognition of abstract patterns (23). Participants were seated in front of a computer and presented with patterns on the computer screen three at a time for a total of 30 target patterns. They were told to try to memorize all the patterns. Each set of patterns was presented for 10 s. A 3.5-min delay was then imposed followed by a four-choice recognition task for the initial stimuli (one of the four stimuli on each recognition trial had been previously seen). Two conditions were presented to each participant. In one condition, the delay period was filled with the administration of the dominant hand condition of the grooved pegboard task. In the other condition, the delay period was filled with administration of additional distractor patterns, presented in the same format as the target stimuli. Subjects were instructed to try to memorize all of the patterns; however, none of the distractor patterns were included in the recognition task. Order of administration for each of these conditions was counter-balanced across subjects. An average accuracy score and average response time (correct responses only) was calculated for the entire task.

Motor speed.

Grooved pegboard: (39) This task assesses fine motor control and speed. Participants had to fit notched pegs into matching holes as quickly as possible. Time taken to fill all holes was recorded for each hand (dominant and non-dominant), and an average time was calculated.

Attention.

Sustain: (40) This task assesses selective and sustained attention for verbal information. Participants sit in front of a computer and were presented with a random string of letters for a total of 8 min. Each letter was presented in the center of the screen for 85 ms with a 900-ms intertrial interval. Participants responded by hitting the space bar whenever a ‘K’ was presented. Average accuracy and reaction time (correct trials only) were calculated.

Analysis.

Our analysis strategy was designed to focus on the task (SDR) that has been related to SH in past studies, while controlling for possible confounding variables. Secondary analyses considered the remaining tasks, which have not been associated previously with SH.

SDR analysis: To address the primary hypothesis, a hierarchical linear regression procedure (SPSS, version 11.0) was performed on all the T1DM subjects. Long-delay SDR performance at follow-up was the dependent variable, and baseline long-delay SDR, age, age of onset, gender, and the presence or absence of SH during the follow-up period were the independent variables. The semipartial correlation coefficient was tested for significance to determine the unique contribution of the presence or absence of SH to follow-up long-delay SDR performance, after differences in baseline performance and effects of gender, age, and age of onset had been removed. Cue-present and short-delay performances were analyzed in a similar manner to determine the specificity of any results. Significance level was Bonferroni corrected for three comparisons and set at $p \leq 0.016$. To determine whether there were any differences between T1DM groups and controls across all SDR conditions, general linear repeated measures analyses and t-tests were also performed.

Secondary task analysis: To determine whether other memory, attention, and motor speed tasks were related to hypoglycemic experiences during the follow-up period, similar hierarchical regression analyses were performed on a limited number of variables hypothesized to be the most likely to be sensitive to SH (SDR: distractor task accuracy; story recall: percent retained; CVLT-C: delayed free recall; DMSL: average accuracy and average response time; grooved pegboard: average time; and sustain: average accuracy). Significance level was Bonferroni corrected for seven comparisons and set at $p \leq 0.007$.

Results

Subjects

Eighty-five subjects (59 T1DM and 26 sibling controls) were enrolled in our study. Nine did not complete the follow-up testing (moved out of state, $n=2$; failed to comply with treatment visits, $n=6$; and control who developed T1DM after baseline, $n=1$). Another nine subjects were excluded from analyses (started Ritalin treatment between testings, $n=3$; significant hyperglycemia during testing, $n=2$; new neurological diagnoses, $n=2$; and technical difficulties, $n=2$). The remaining 67 subjects included 42 T1DM subjects and 25 sibling controls. Groups were not different in age (T1DM: mean = 11.6, SD = 2.6; control: mean = 11.9, SD = 2.8; and t -test: $t = -0.45$, $p = 0.66$) or in mean parental education (T1DM: mean = 14.4, SD = 2.1; control: mean = 14.7, SD = 1.9; and t -test: $t = -0.64$, $p = 0.53$).

T1DM patients were then divided into two groups: Those who had experienced at least one SH episode ($n=14$) and those who did not experience any SH episodes ($n=28$). Details concerning their hypoglycemic experiences are below. These groups did not differ (t -tests) from each other in age of onset ($p=0.61$), number of SH ($p=0.63$) or hyperglycemic episodes ($p=0.10$) experienced between diagnosis and baseline testing, or number of hyperglycemic episodes experienced between baseline and follow-up ($p=1.0$). The proportion of patients undergoing IT and UC treatments was similar across SH groups (chi-square, $p=0.48$). In addition, groups were not different in HbA1c levels taken just before baseline ($p=0.94$) or follow-up ($p=1.0$) sessions, or in average HbA1c during the follow-up period ($p=0.25$) (Table 1).

The T1DM groups were not different from each other or from the sibling control group in age, duration of follow-up (t -tests, $p > 0.40$), or gender distributions (chi-square, $p > 0.40$) (Table 1).

Severe glycaemic events

The median number of SH episodes that the SH group experienced was 1.0 (range = 1–5; total number of events = 27). All episodes involved inability to self-treat, response to treatment (six or 22% with glucagon, two or 7% with intravenous glucose administration, and the rest with food or drink) and most (23 or 89%) had reported clear neurological symptoms (e.g., incoherence, disorientation, failure to arouse, impaired speech, dis-coordination, seizures, two or 7%, and loss of consciousness, six or 22%). Those episodes without reported clear neurological symptoms had verified low glucose levels and inability to self-treat. No episodes occurred within 24 h of cognitive testing. Three subjects (7%) each had one severe hyperglycemic episode in between baseline and follow-up.

SDR analyses

T1DM groups.

The presence of hypoglycemic SH episodes between baseline and follow-up in the T1DM group accounted for a unique and significant portion of the variance in follow-up long-delay SDR performance after controlling for baseline performance, age, age of onset, and gender ($p=0.017$) (Table 2). Additionally, there was a relationship between age ($p=0.01$), but not age of

Table 1. Demographic and clinical characteristics of unmatched type 1 diabetes mellitus (T1DM) subgroups and sibling controls

	T1DM with SH	T1DM without SH	Sibling controls
N	14	28	25
Age (yr)	11.3 (2.7)	11.7 (2.6)	11.9 (2.8)
Gender (male/female)	7/7	12/16	15/10
Parental education (yr)	14.3 (2.2)	14.4 (1.2)	14.7 (1.9)
Number of months of follow-up	15.9 (3.4)	14.7 (2.4)	15.7 (4.7)
Age of onset	6.4 (3.7)	7.0 (3.4)	–
SH episodes prior to baseline testing	2.7 (2.2)	2.4 (3.0)	–
Median	2.5	1.0	–
Range	0–7	0–12	–
SH episodes between baseline and follow-up			
Median	1	0	–
Range	1–5	0	–
Severe hyperglycemic episodes prior to baseline testing	6.5 (4.6)	3.4 (1.3)	–
Median	4	3	–
Range	1–20	0–11	–
Severe hyperglycemic episodes between baseline and follow-up			
Median	0	0	–
Range	0–1	0–1	–
HbA1c at baseline	8.2 (1.0)	8.2 (1.1)	–
Mean HbA1c during follow-up	8.6 (0.8)	8.2 (1.1)	–
HbA1c at follow-up	8.5 (1.2)	8.5 (1.5)	–

SH, severe hypoglycemia. Values are means (SD), except as noted.

Table 2. Hierarchical regression results for all type 1 diabetes mellitus subjects

Dependent variable	Beta	R ²	t	Semipartial r	p
SDR long-delay error	-0.32	0.09	-2.50	-0.38	0.017
SDR short-delay error	-0.13	0.02	-0.87	-0.14	0.39
SDR cue-present error	-0.31	0.09	-2.23	-0.31	0.03
Story recall, verbatim percent retained	-0.11	0.01	-0.69	-0.12	0.49
Grooved pegboard average time	0.00	0.00	0.04	0.01	0.97
CVLT-C long-delay free recall	0.10	0.01	0.78	0.13	0.44
SDR distractor task accuracy	0.00	0.01	0.05	0.01	0.96
DMSL average accuracy	0.03	0.18	1.33	0.19	0.22
DMSL average reaction time	0.06	0.24	1.76	0.29	0.09
Sustain average accuracy	-0.11	0.01	-0.83	-0.10	0.41

CVLT-C, California verbal learning task – children's version; DMSL, delayed match to sample, list presentation; SDR, spatial delayed response; SH, severe hypoglycemia. Semipartial r reflects unique relationship between the presence of SH between baseline and follow-up sessions and performance on the dependent variable after effects of baseline performance, age, age of onset, and gender have been statistically removed.

onset ($p = 0.44$), and follow-up long-delay SDR performance after controlling for baseline performance. Mean long-delay SDR performance adjusted for age, age of onset, and gender is shown for the T1DM groups in Figure 1 and Table 3.

In further hierarchical regression analyses, presence of SH was not significantly related to follow-up short-delay SDR performance within the T1DM subjects (Fig. 2, Table 2). However, it was related to follow-up cue-present SDR performance, although this p-value ($p = 0.03$) was not below our Bonferroni's threshold (Fig. 2, Table 2). In order to determine whether differences in overall pointing error could explain our findings with the long-delay SDR performance, another hierarchical regression procedure was performed on the follow-up long-delay SDR performance that included cue-present SDR performance (both baseline and follow-up) as another covariate. After removing the effects of cue-present performance, baseline long-delay performance, age, and age of onset, long-delay

follow-up performance was still significantly associated with presence of SH (beta = -0.27, R² change = 0.06, $t = -2.0$, $p = 0.05$, semipartial $r = -0.25$).

Matched T1DM groups.

Despite using hierarchical regression to control for baseline performance, differences between the two T1DM groups at baseline may affect our findings. Thus, as a secondary analysis, we matched subjects in the two T1DM groups on baseline performance. Matching was done on a case-by-case basis; long-delay SDR performance for a pair of subjects had to be within 5 mm. This process resulted in 13 pairs of subjects (one T1DM with SH and the largest SDR long-delay error did not have a match). Mean age, age of onset, gender distribution, and baseline long-delay SDR were all comparable ($p > 0.05$; Table 4). These data were then subjected to a hierarchical linear regression with baseline performance, age, age of onset, and gender as covariates. This analysis found a significant effect of SH on performance at follow-up (beta = -0.38, R² change = 0.13, semipartial $r = -0.36$, $t = -2.4$, $p = 0.03$).

Despite similar baseline performance, the T1DM group with SH became less accurate, while the T1DM group without SH got more accurate at follow-up. Comparisons between baseline and follow-up performance were performed within each group to determine relative effect sizes (repeated measures general linear models with age, age of onset, and gender as covariates). These analyses revealed a larger effect size for the T1DM without SH group than that for the T1DM with SH group (partial ϵ^2 ; T1DM without SH = 0.16; T1DM with SH = 0.03).

Hierarchical regression analyses on cue-present and short-delay performance revealed no significant relationship between the T1DM group and performance at follow-up (cue present: beta = -0.16, R² change = 0.02, semipartial $r = -0.15$, $t = -0.91$, $p = 0.37$; short delay: beta = -0.17, R² change = 0.02, semipartial $r = -0.15$, $t = -0.98$, $p = 0.34$). In total, these results suggest that

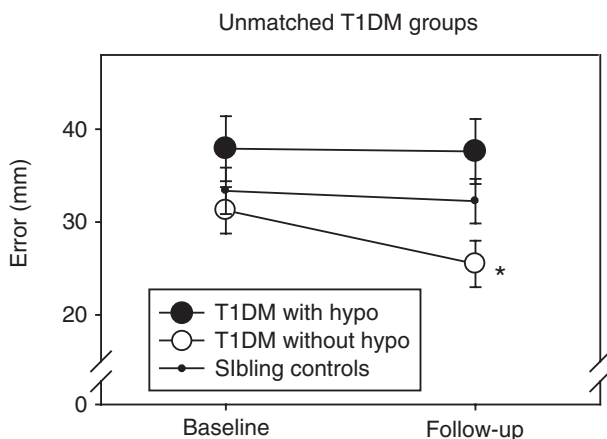


Fig. 1. Spatial delayed response mean (\pm SEM) performance at baseline and follow-up for unmatched type 1 diabetes mellitus (T1DM) groups and sibling controls. Means are adjusted for age, age of onset, and gender for the T1DM groups and age and gender for the sibling control group. *T1DM without severe hypoglycemia (SH) performed significantly better than the T1DM with SH group at follow-up in both unmatched and unmatched analyses.

Table 3. Cognitive variables means (SEM) adjusted for age, gender and age of onset in type 1 diabetes mellitus (T1DM) and adjusted for age and gender in sibling control group

	T1DM with SH (n = 14)		T1DM without SH (n = 28)		Sibling control (n = 25)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Cue-present error (mm)	2.4 (0.3)	2.2 (0.3)	2.3 (0.2)	1.5 (0.2)	3.1 (0.3)	1.8 (0.2)
Short-delay error (mm)	23.4 (2.3)	19.3 (1.1)	19.5 (1.7)	18.0 (0.7)	18.4 (1.5)	17.5 (0.8)
Long-delay error (mm)	38.0 (3.5)	37.9 (3.6)	31.2 (2.5)	25.4 (2.5)	33.5 (2.4)	32.5 (2.4)
Distractor task accuracy	0.96 (0.01)	0.98 (0.01)	0.99 (0.01)	0.99 (0.01)	0.98 (0.01)	0.99 (0.01)
Story recall, percent retained	1.02 (0.04)	0.94 (0.04)	0.96 (0.03)	0.90 (0.02)	0.92 (0.03)	0.95 (0.02)
DMSL accuracy	0.61 (0.04)	0.59 (0.04)	0.56 (0.02)	0.63 (0.03)	0.58 (0.03)	0.61 (0.03)
DMSL response time (ms)	4044 (275)	3673 (229)	4307 (187)	4207 (156)	4150 (198)	4083 (174)
CVLT-C long-delay, free recall	12.0 (0.6)	12.0 (0.5)	11.5 (0.4)	12.3 (0.4)	11.1 (0.4)	12.4 (0.3)
Grooved pegboard, time to complete (s)	92.1 (4.5)	82.6 (4.8)	80.6 (3.8)	73.5 (3.4)	80.7 (2.4)	74.6 (1.9)
Sustain accuracy	0.88 (0.02)	0.93 (0.02)	0.94 (0.02)	0.94 (0.02)	0.94 (0.01)	0.94 (0.01)

CVLT-C, California verbal learning task – children's version; DMSL, delayed match to sample, list presentation; SH, severe hypoglycemia.

follow-up long-delay SDR performance was influenced more by events that occurred during the follow-up period (e.g., SH) than events that occurred prior to baseline measurements.

Sibling controls vs. T1DM groups.

To determine differences in performance from the non-diabetic control group, a hierarchical analysis was performed on long-delay SDR performance at follow-up that included all three groups, covarying out baseline performance age and gender. The relationship between group and SDR long-delay performance at follow-up was not significant ($p > 0.05$).

Comparisons were also performed between groups on baseline and follow-up long-delay SDR performance using a univariate analysis, covarying age and gender. At baseline, there was no significant main effect of group [$F(2, 62) = 1.2, p = 0.25$]. However, at follow-up, the main effect of group was significant [$F(2, 62) = 5.4, p = 0.007$]. Between group *post hoc* comparisons revealed a significant difference between the T1DM group without SH and both of the other groups ($p < 0.05$), but not between the T1DM with SH and controls ($p = 0.19$) (Fig. 1).

Hyperglycemia.

Analyses on the effect of severe hyperglycemic episodes or hypoglycemic seizures on performance was not meaningful because of the small number of events (Table 1).

Secondary cognitive measures.

None of the task variables selected, other than long-delay SDR, was significantly associated with number of previously experienced SH episodes in hierarchical regression analyses. Results from these analyses are summarized in Table 2, and mean and SD for each cognitive variable for the T1DM subgroups are summarized in Table 3.

Conclusions

In this prospective study, SH was associated with poorer performance on a spatial long-term memory task in children with T1DM, confirming results from our previously reported retrospective study (22). T1DM children with SH tended to perform the same at both time points, whereas T1DM children without SH tended to improve their performance at follow-up, presumably from age-related cognitive gains or experience with the testing procedure. As seen in several of

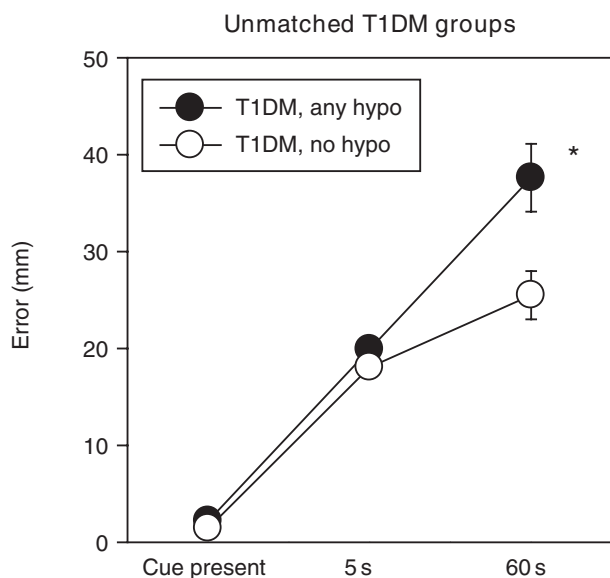


Fig. 2. Spatial delayed response (SDR) mean (\pm SEM) performance across three delays (cue present, 5s, and 60s) for unmatched type 1 diabetes mellitus (T1DM) groups at follow-up. Means are adjusted for baseline performance, age, gender, and age of onset for the T1DM groups. *Groups performed significantly different on long-delay SDR only.

Table 4. Demographic and clinical characteristics of type 1 diabetes mellitus (T1DM) subgroups matched for baseline spatial delayed response (SDR) long-delay performance

	T1DM with SH	T1DM without SH
N	13	13
Age (yr)	11.5 (2.7)	10.7 (3.0)
Gender (male/female)	6/7	6/7
Parental education (yr)	14.5 (2.2)	14.6 (1.2)
Number of months of follow-up	15.8 (4.5)	14.9 (4.8)
Age of onset	6.6 (3.7)	6.6 (3.7)
SH episodes prior to baseline testing	2.4 (1.9)	2.5 (3.0)
Median	2.0	1.0
Range	0–5	0–9
SH episodes between baseline and follow-up		
Median	1	0
Range	1–5	
Severe hyperglycemic episodes prior to baseline testing	6.9 (5.6)	3.0 (2.7)
Median	5	2
Range	1–20	0–9
Severe hyperglycemic episodes between baseline and follow-up		
Median	0	0
Range	0–1	0–0
HbA1c at baseline	8.2 (1.1)	8.1 (11)
Mean HbA1c during follow-up	8.6 (0.8)	8.2 (1.0)
HbA1c at follow-up	8.5 (1.2)	8.2 (0.7)
Follow-up SDR cue present	2.2 (0.3)	1.5 (0.2)
Follow-up SDR 5 s delay	19.1 (1.1)	18.0 (0.7)
Follow-up SDR 60 s delay	37.0 (3.6)*	25.8 (2.5)

SH, severe hypoglycemia. Values are means (SD), except as noted.

*T1DM groups were different on SDR long-delay performance at follow-up ($p = 0.03$). SDR means (SEM) are adjusted for baseline long-delay performance, age, gender, and age of onset.

our previous studies, this relationship was specific to long-term spatial memory; no effect of SH was observed on short-term spatial memory, verbal and object memory tasks, or on attention and motor speed tasks (23, 41). Other groups have also reported varying degrees of specificity of SH effects on memory (26, 28).

In the current study, spatial memory was more sensitive to SH than verbal memory. Spatial skills may be more affected than verbal skills by early developmental neural insults (42, 43), and this pattern may also exist for memory function following early medial temporal insults (20). In addition, visuospatial function and spatial memory may be preferentially impaired by SH in T1DM children (28, 44, 45). Our data are more consistent with a specific effect of SH on spatial memory because: 1) after partialing out the effect of performance on a visuomotor control condition (SDR cue present), the significant relationship between SH and long-delay performance remained; 2) short-term spatial memory performance (short-delay SDR) was not affected by SH; 3) in our matched sample analyses, visuomotor performance (SDR cue present) was not affected by SH but long-delay spatial memory was; and 4) in a more recent unpublished study, we again found an effect of SH on long-delay SDR, but not on a spatial intelligence test (WJ-III Spatial Relations; Hershey et al. unpublished data). However, future studies may attempt to better disentangle spatial memory from general visuospatial function as they relate to the SDR task.

Alternatively, long-delay SDR performance may be a better measure of the effects of SH on the brain than other tasks, regardless of the type of stimuli used. Long-delay conditions on delayed response tasks have been more thoroughly validated as measures of medial temporal integrity than other standard memory tasks. Thus, if SDR is a 'purer' measure of medial temporal function, it may be harder for individuals to compensate on this task than on less-specific, more multifactorial tasks. In addition, there are other variables that differ between SDR and the verbal memory tasks used in this study (story recall and CVLT-C), including the level of semantic structure in the material and whether or not unique or repeated stimuli are used across trials. These variables may contribute to different levels of sensitivity across tasks. Clearly, conclusions about SH effect on cognitive function depend in part on the measures used. To make strong comparisons across different types of material (e.g., verbal vs. spatial vs. object), psychometrically equivalent and well-validated memory tasks need to be developed.

In the current and a previous study (22), we found significant differences between T1DM patients with and without SH on long-delay SDR performance. However, T1DM patients with SH were not substantially worse than sibling controls in either study (although there was some overlap between the two studies in group membership). It is difficult to place this finding in the context of other results, because statistical comparisons between sibling controls and T1DM groups with and without

SH have not been reported (26, 28). Interestingly, a recent, very large study found that T1DM children actually had higher academic achievement than their sibling controls. This difference diminished with worse glycemic control (46). This pattern is roughly similar to our findings. In a more detailed analysis of the impact of diabetic variables such as SH on academic achievement, the authors did not report statistical comparisons to sibling control performance (47). Thus, it remains unclear as to what degree of SH exposure is required to produce impairment compared to sibling controls in children with T1DM. One possibility is that sibling controls may differ in unanticipated ways from non-related controls that somehow reduces their cognitive performance. Future studies may want to include both types of control groups to clarify this issue. Finally, to answer our primary question in this study, how SH, rather than T1DM, affects cognitive outcome, a T1DM group without SH is the most appropriate control group.

The effect of SH on spatial long-delay performance in this sample probably does not reflect a clinically apparent memory impairment. However, the effect of SH on memory was significant, patients were followed for only 15 months, the number of SH events experienced was limited, and we have seen this same relationship in previous work. Based on this information, we believe that this effect is reliable, and we would predict that greater SH exposure could eventually produce clinically detected spatial and possibly verbal memory deficits potentially affecting educational or occupational functioning, as suggested by recent work by McCarthy (47) [but see (31)]. This prediction could be tested in a larger, more diverse sample with a longer follow-up period using experimental and clinical measures of memory function. Such efforts could better characterize the dose-response effect of SH, help determine the link between experimental cognitive tasks (e.g., SDR) and behavior in real world settings (e.g., school) and determine whether SH interferes with normal developmental gains or with the ability to benefit from practice or both.

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