Explicit memory performance in infants of diabetic mothers at 1 year of age

Tracy DeBoer PhD, Institute of Child Development and Center for Neurobehavioral Development;
Sandi Wewerka MPH, Institute of Child Development;
Patricia J Bauer PhD, Institute of Child Development and Center for Neurobehavioral Development;
Michael K Georgieff MD;
Charles A Nelson* PhD, Department of Pediatrics, Institute of Child Development and Center for Neurobehavioral Development, University of Minnesota, USA.

**Correspondence to last author at* Developmental Medicine Center, Boston Children's Hospital, 300 Longwood Avenue, Fegan 10, Harvard Medical School, Boston, MA 02115, USA.
E-mail: canelson@umn.edu

The aim of the present research was to investigate the impact of abnormal fetal environment on explicit memory performance. Based on animal models, it was hypothesized that infants of diabetic mothers (IDMs) experience perturbations in memory performance due to exposure to multiple neurologic risk factors including: chronic hypoxia, hyperglycemia/reactive hypoglycemia, and iron deficiency. Memory performance, as measured by the elicited/deferred imitation paradigm, was compared between 13 IDMs (seven females, six males; mean age 365 days, SD 11) and 16 typically developing children (seven females, nine males; mean age 379 days, SD 9). The IDM group was characterized by shorter gestational age (mean 38w, SD 2), greater standardized birthweight scores (mean 3797g, SD 947), and lower iron stores (mean ferritin concentration 87μg/L, SD 68) in comparison with the control group (mean gestational age: 40w, SD 1; mean birthweight: 3639g, SD 348; mean newborn ferritin concentration 140μg/L, SD 46). After statistically controlling for both gestational age and global cognitive abilities, IDMs demonstrated a deficit in the ability to recall multi-step event sequences after a delay was imposed. These findings highlight the importance of the prenatal environment on subsequent mnemonic behavior and suggest a connection between metabolic abnormalities during the prenatal period, development of memory, circuitry, and behavioral mnemonic performance.

See end of paper for list of abbreviations.

Infants of diabetic mothers (IDMs) comprise a compelling group in which to examine associations between fetal risk factors and subsequent memory performance. The adverse environment associated with diabetic pregnancy consists of multiple neurologic risk factors including: (1) chronic hypoxia (Widness et al. 1981), (2) hyperglycemia/reactive hypoglycemia, and (3) iron deficiency (Petry et al. 1992), which, on the basis of animal models, have been shown to act selectively on regions of the fetal brain that are involved in explicit memory (e.g. the hippocampus; Barks et al. 1995, de Ungria et al. 2000). Based on the known pathophysiology, it is hypothesized that exposure to these risk factors during the prenatal period may alter memory performance in human infants (see Georgieff and Rao 2001 for review).

Several studies have demonstrated that neurobehavioral outcomes in human children who were born to mothers with diabetes are inversely correlated with the quality of metabolic regulation during pregnancy (Rizzo et al. 1997). However, these investigations have typically examined *global* cognitive development in children long after the proposed insult, and are not necessarily related to specific risk factors or areas of injury. The purpose of the present research was to further characterize outcomes related to development in an abnormal prenatal environment by examining the relation between IDM's prenatal environment and behavioral explicit memory performance using the elicited imitation paradigm.

RISK FACTORS

Prenatal hypoxia and hyperglycemia/reactive hypoglycemia have been associated with poor behavioral and neurologic outcomes. Specifically, prenatal hypoxia is linked with motor and cognitive deficits in humans (Low et al. 1984) and damage to memory areas, such as the cerebral cortex, striatum, and hippocampus, in animal models (Nelson and Silverstein 1994). Severe postnatal hyperglycemia/reactive hypoglycemia are linked with impairments in both cognitive functioning and learning in humans (Hannonen et al. 2003), and animal models have demonstrated that certain regions of the brain (e.g. the hippocampus) show particular vulnerability (Barks et al. 1995). When these risk factors co-occur, as in the diabetic pregnancy, oxygen consumption of the fetus increases and renders the fetus hypoxemic (Widness et al. 1981), which can result in brain iron deficiency through shifting of available fetal iron away from the brain and into the expanding red cell mass (Petry et al. 1992). In short, gestational diabetes mellitus introduces multiple risk factors to the developing fetus, each of which has been shown to have independent effects on neurodevelopment and, thus, may affect mnemonic behavior.

ELICITED IMITATION

Elicited imitation involves using novel toys to produce an action or a sequence of actions that the infant imitates. It is generally accepted as a non-verbal analog to hippocampally-mediated verbal recall, and has been used in numerous studies to assess explicit memory abilities in preverbal infants (Bauer 2005). One of the most compelling arguments in support of the analogy is the finding that adults with amnesia who sustained damage to the hippocampal region are unable to perform an age-appropriate version of the task (McDonough et al. 1995); developmental amnesiacs show similar deficits (Adlam et al. 2005, Bauer 2005).

The elicited imitation paradigm can be modified to produce

a battery of nonverbal mnemonic tasks resembling several explicit memory tasks in the adult: (1) immediate imitation as an index of short-term recall, (2) deferred imitation as an index of long-term recall mediated by the hippocampally-dependent explicit memory system, and (3) interleaved presentation as a measure of working memory, i.e. steps of one sequence are presented interspersed with steps from another sequence (Bauer 2005). Immediate imitation performance is subject to rapid decay and does not correlate with recall performance following delays (10 minutes to 48 hours in length; Bauer et al. 1999); therefore, immediate imitation is argued to be mediated by a short-term memory store, represented by a temporary pattern of activation. In contrast, deferred imitation is mediated by a representational system that requires the transfer of the information from short-term storage into something more durable, such as the hippocampally-mediated memory system. Finally, when the presentation of the to-be-remembered sequences is interleaved, a working memory requirement is imposed and the infant must hold in mind the individual steps of the events as they integrate the information over time.

The present investigation aimed to examine whether: (1) IDMs exhibited deficits in explicit memory performance at the end of the first year of life, (2) any observed deficits were specific to explicit memory or were pervasive across general memory processes, and (3) if any of the specific risk factors appeared to be associated with memory ability.

Table I: Medical criteria for inclusion in study

No pregnancy complications
Lack of intrauterine growth restriction, significant maternal hypertension, chromosomal syndromes/non-chromosomal congenital anomalad sequences, and congenital infectious agents (TORCH)
Normal labor and delivery
No significant heart rate decelerations and 5 minute Apgar scores >6
Uncomplicated neonatal course
No mechanical ventilation and no indication of acute perinatal or neonatal insult, such as asphyxia, sepsis, seizures, meningitis, or intracranial hemorrhage

Method

PARTICIPANTS

Forty-three 12-month-old infants (14 IDMs, 29 controls) who were enrolled in a longitudinal research project investigating prenatal risk factors on cognitive development participated in the investigation. The sample consisted of predominately Caucasian infants (91%) born to families of middle to high socioeconomic status (for other reports on this sample see deRegnier et al. 2000; Nelson et al. 2000, 2003; Georgieff et al. 2002; DeBoer et al. 2004; Siddappa et al. 2004).

Pregnant women were recruited at 28 weeks' gestation from United Hospital Children's Hospital of St Paul, University of Minnesota/Fairview Riverside Medical Center, or Abbott-Northwestern Hospital, USA. In addition to meeting the medical criteria shown in Table I, infants born to women diagnosed with diabetes mellitus were eligible for inclusion in the IDM sample if they were delivered at 32 weeks' gestation or more and had an uncomplicated neonatal course. Infants in the control group were eligible if pregnancies were uncomplicated by diabetes, were 36 to 41 weeks' gestation, and if birthweight was appropriate for gestational age. At time of delivery, infants were assessed for signs of iron deficiency by means of cord serum ferritin concentrations and exposure to hypoxia and hyperinsulinemia by means of neonatal macrosomia (Morris et al. 1985, Akin et al. 2002). Ferritin values less than 76μg/L were considered deficient in fetal iron stores (Tamura et al. 2002) and size for dates (i.e. birthweight *z*-scores) greater than 2 standard deviations (SDs) above the population mean suggested the presence of chronic fetal hypoxia and hyperinsulinemia (Nold and Georgieff 2004). Eleven control infants were excluded from the sample due to unknown ($n=5$) or low (<76μg/L; $n=6$) ferritin concentrations. Comparisons between the groups indicated that the IDM group had greater birthweight *z*-scores (mean 1.8, SD 2.1) than the control group (mean 0.43, SD 0.75), $F(1,27)=6.05$, $p<0.05$, and lower newborn ferritin concentrations[1] (mean 87μg/L, SD 68) relative to the control group (mean 140μg/L, SD 46), $F(1, 27)=6.17$, $p<0.05$.

[1]Consistent with previous reports (Georgieff et al. 2002), postnatal follow-up assessments of iron status between 6 and 12 months of age indicated that no infant born with low iron stores had iron deficiency at one year of age, as all measured ferritin concentrations were within the normal range (21–88μg/L) and did not significantly differ between the two groups ($p=0.89$).

Table II: Summary of group characteristics

Characteristic	*Control Mean (SD)*	*IDM Mean (SD)*	*F statistic of one-way ANOVA or χ^2 statistic*
Gestational age at birth, wks	40 (1)	38 (2)	$F(1,27)=7.21, p<0.05$
Birthweight, g	3639 (348)	3797 (947)	*ns*
Birthweight *z*-scores	0.43 (0.75)	1.8 (2.1)	$F(1, 27)=6.05, p< 0.05$
Birthweight *z*-scores >2	0/16	7/13	$\chi^2(1, N=29)=11.36, p<0.01$
Prenatal (newborn) Ferritin, μg/L	140 (46)	87 (68)	$F(1,27)=6.17, p<0.05$
Ferritin ≤76mg/L	0/16	6/13	$\chi^2(1, N=29)=9.31, p<0.01$
Postnatal (6–12 month) Ferritin, μg/L	46 (21)	48 (26)	*ns*
Age at test, days	365 (11)	379 (9)	*ns*
Age at Bayley, days	380 (14)	379 (11)	*ns*
Bayley Scales: MDI	103 (10)	95 (8)	$F(1,27)=5.50, p<0.05$
Bayley Scales: PDI	102 (13)	89 (21)	$F(1,26)=3.93, p=0.06$

Bayley scales, Bayley Scales of Infant Development, 2nd edition (Bayley 1993); IDM, infants of diabetic mothers; MDI, mental development index; *ns*, not significant; PDI, psychomotor developmental index.

Infants who developed significant postnatal conditions affecting growth and development ($n=3$) or whose data were not available due to equipment failure ($n=1$) were excluded from the analyses.

The final sample consisted of 29 infants: 13 IDMs (seven females, six males) and 16 control infants (seven females, nine males). Mean corrected age at the elicited imitation session was approximately 12 months (367 days SD 10; range 350–385) and there were no age differences between the groups ($p=0.25$). See Table II for a summary of group characteristics.

PROCEDURE

Each test event was drawn from an existing pool of 11 different events (listed in Table III) and counterbalanced across task and participants. The events consisted of two target actions that produced an interesting and desirable end state (example shown in Figure 1).

All infants participated in two individual testing sessions that lasted approximately one hour each. Caregivers were present during both the testing sessions, but were not permitted to assist their children with the task. At the end of each session, children received a small gift and caregivers were reimbursed for transportation costs. Ethical permission for the study was obtained from the recruitment hospitals and from the University of Minnesota; informed consent was obtained from the caregivers of the participating infants.

Table III: Each child was tested with six out of the following 11 events. Event sequences were counterbalanced across task and participants

Event	*1st target action*	*2nd target action*	*End state*
Make a Glowball	'Open the lid'	'Pull out the drawer'	Glowball lights up
Make a Gong	'Hang up the bell'	'Ring it'	Gong rings
Turn on the light	'Put in the car'	'Push the stick'	Light turns on
Find Bubbles	'Put in the block'	'Push it in'	Bubbles pop out
Make a Happy Face	'Open the door'	'Push in the block'	Happy face appears
Find the Bear	'Slide the bar'	'Open the door'	Bear appears
Make a Balloon	'Put in the balloon'	'Press it'	Balloon blows up
Make an Airplane	'Unfold it'	'Fly it'	Airplane flies
Make a Rattle	'Cover it'	'Shake it'	Rattle shakes
Make a Jumper	'Push in the ball'	'Pop it'	Ball jumps
Make the Duck Walk	'Put down the ramp'	'Go for a walk'	Duck slides down ramp

a

b

Figure 1: *Photographs of infant completing event sequence 'Turn on the light.' (a) Infant places a small car into track of an L-shaped apparatus. (b) Infant pushes a plunger, causing car to travel down the track which trips a small switch and causes a light to illuminate. (Reproduced with permission from Bauer et al. 2003)*

ELICITED IMITATION

One of two trained researchers (authors TD and SW) conducted each elicited imitation session. After a period of free play, six different events were presented to the infant: two events that the infants were allowed to imitate immediately (the immediate imitation task), two events they were allowed to imitate after a 10-minute delay (the deferred imitation task), and two events in which the individual target actions of the two different events were presented interleaved with one another (the interleaved imitation task). See Table IV for a schematic of the experimental design.

The immediate imitation task consisted of an infant-controlled baseline phase during which the infant was given general prompts (e.g. 'What can you do with this stuff?'). This was followed by modeling of the sequence twice in succession with narration, and an opportunity for immediate imitation prompted by a verbal reminder (i.e. the name of the event sequence; see Bauer 2005). The deferred imitation task also consisted of a baseline phase, followed by modeling. However, a delay of approximately 10-minutes was imposed before the infant was allowed to imitate. The 10-minute delay imitation was 'filled': during the delay the infants experienced the baseline and imitation phases of the immediate imitation task with different event sequences (Bauer et al. 1999). After the delay, the infants were given each set of props in turn and encouraged to imitate the actions. The baseline phase served as a control for general problem-solving skills or production of the sequences by chance. Imitation served as the dependent measure of recall. Finally, the interleaved imitation task consisted of the alternating modeling of the two events, followed by imitation. No baseline measure was used in this task as it is an analog to a working memory task, and as the cognitive processes of interest were the binding and integration of the information over time. If the elements of the sequence had been presented before modeling, one could not have been certain that the processes were carried out during modeling.

Table IV: Presentation of event sequences

Baseline	*Modeling*	*Recall*
Deferred 1	Deferred 1	
Deferred 2	Deferred 2	
Immediate 1	Immediate 1	Immediate 1
Immediate 2	Immediate 2	Immediate 2
		Deferred 1
		Deferred 2
	Interleaved 1–1	
	Interleaved 2–1	
	Interleaved 1–2	
	Interleaved 2–2	
		Interleaved 1
		Interleaved 2

Infants were presented with six event sequences. For two sequences infants were allowed to imitate immediately after baseline and modeling (Immediate 1 and 2); for two sequences there was a 10-minute delay before imitation (Delay 1 and 2); and presentation of two sequences was interleaved such that infants saw first step of Sequence 1, first step of Sequence 2 (Interleaved 1–1, Interleaved 1–1), then second step of Sequence 1 and second step of Sequence 2 (Interleaved 1–2, Interleaved 2–2) before imitation was permitted.

SCORING

Infants' performance on the imitation tasks were videotaped and coded off-line by trained observers who were unaware of the group identity and the hypotheses of interest. Each task yielded two dependent measures: (1) the number of individual target actions produced, and (2) the ordered recall of those actions. In calculating the latter measure only the first occurrence of each target action was considered, which reduced the likelihood that production of a sequence by chance or by trial and error would be credited to the child's performance. For purposes of reliability, 20% of the tapes were coded by a second trained observer. Mean per cent agreement between the coders was 90.47% (range 70.59–100%). When disagreements occurred, observations of the primary observer were used.

BAYLEY SCALES OF INFANT DEVELOPMENT

To assess overall developmental functioning, the Bayley Scales of Infant Development, 2nd edition (Bayley 1993) were administered to infants in both groups within approximately three weeks (mean 13, SD 11 days) of the elicited imitation session by one of two trained individuals (an occupational therapist or clinical psychology graduate student) who were unaware of the group status. Two scores were derived from the Bayley Scales to index the infant's levels of cognitive, language, personal-social, and fine and gross motor development: the mental development index (MDI) and the psychomotor developmental index (PDI).

TREATMENT OF MISSING DATA

In a small number of cases ($n=4$), data were missing at random (e.g. equipment failure, missed appointment). Due to the large individual differences in performance on these tasks and the interest regarding group differences, these data points were coded as missing and excluded from the analyses.

Results

PRELIMINARY ANALYSES

Gestational age

On average, infants in the IDM group were born earlier (mean 38 weeks, SD 2) than infants in the control group (mean 40 weeks, SD 1), $F(1, 27)=7.21$, $p<0.05$. Although this difference is not surprising (given that optimal management of diabetic pregnancy is to deliver between 37 and 38 weeks; see Nold and Georgieff 2004), previous research with slightly older infants has suggested that memory performance may vary as a function of gestational age (see de Haan et al. 2000); therefore, gestational age was entered as a covariate in all elicited imitation analyses.

Effects of overall cognitive development (Bayley Scales of Infant Development)

Results indicated that there was a significant difference between the IDM and control groups' performance on the MDI subscale, with IDMs (mean 95, SD 8) performing significantly below controls (mean 103, SD 10): $F(1,27)=5.50$, $p<0.05$. Differences between the groups' performance on the PDI subscale was marginal, with the IDM group (mean 89, SD 21) performing below the control group (mean 102, SD 13: $F(1,26)=3.93$, $p=0.06$). As these results suggested differences in global cognitive functioning between the two groups, individuals' MDI scores were also entered as a covariate in the analyses of elicited imitation performance to isolate explicit memory performance from general cognitive ability.

Baseline elicited imitation measures

There was not a significant group difference in the baseline levels of performance for either dependent measure (all p values >0.27; Table V, Baseline). Consequently, variation in long-term recall capabilities between the groups cannot be solely attributed to group differences in problem solving abilities.

Recall performance

Across groups, paired samples t-tests revealed that infants learned and retained information regarding both target actions and the order of the actions. For all three imitation tasks, performance was significantly greater during imitation than at baseline[2] ($p<0.05$; see Table V for descriptive statistics).

When effects of group on recall performance were investigated, controlling for both gestational age and cognitive abilities, no significant group effect was found for production of target actions in the immediate, deferred, or interleaved imitation tasks. Also, no significant group effect was found for production of pairs of target actions in either the correct temporal order in the immediate or interleaved imitation tasks (all $p>0.15$). However, the two groups performed differently on recall of target actions in the correct temporal order after a 10-minute delay: $F(1, 22)=4.44, p<0.05$. Thus, although the IDM group did not produce fewer total actions than the control group, the actions they did produce were not in the correct temporal order (see Fig. 2). Specifically, six out of 16 controls produced more pairs of actions at recall than at baseline ($p<0.05$; 10 ties), whereas only one out of 11 IDMs produced more pairs of actions at recall than at baseline ($p=1.0$; 9 ties, 1 negative difference).

Finally, in order to determine if the differential performance

[2]The average of the baseline for the immediate and deferred recall task was used for the interleaved imitation task.

Table V: Descriptive statistics of target actions and pairs of actions at baseline and recall

Condition/task/group	*Measure*			
	Target actions		*Pairs of actions (ordered recall)*	
	Mean	*SD*	*Mean*	*SD*
Baseline				
Immediate				
Control	0.50	0.37	0.03	0.13
IDM	0.54	0.45	0.00	0.00
10-min deferred				
Control	0.72	0.45	0.06	0.17
IDM	0.50	0.56	0.04	0.14
Recall				
Immediate				
Control	1.2	0.58	0.38	0.34
IDM	0.96	0.65	0.23	0.34
10-min deferred				
Control	1.1	0.64	0.31[a]	0.36
IDM	0.85	0.47	0.05[a]	0.16
Interleaved				
Control	1.2	0.60	0.25	0.32
IDM	1.0	0.48	0.13	0.23

[a]$p<0.05$. IDM, infants of diabetic mothers.

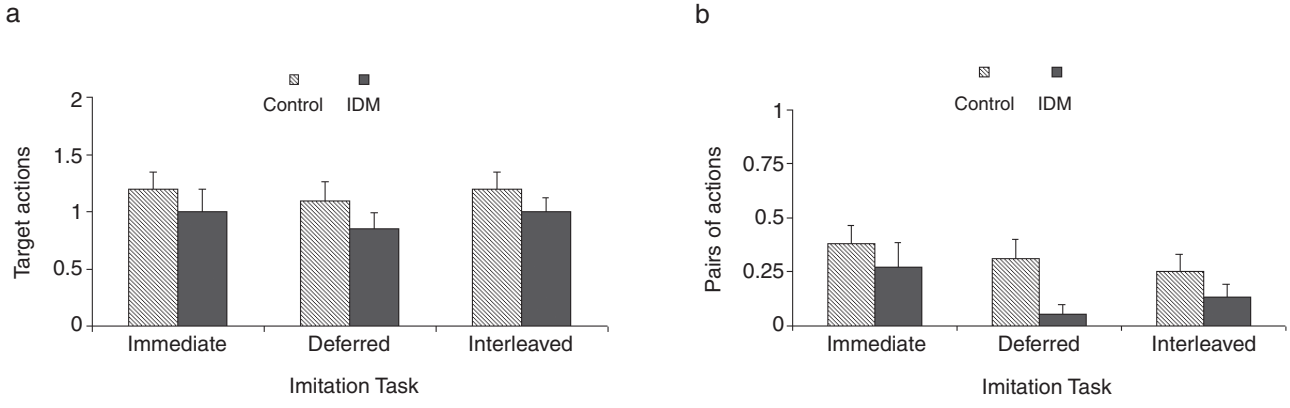

Figure 2: *Mean (+1 standard error of mean) (a) number of target actions and (b) correctly ordered pairs of actions produced during the immediate, deferred, and interleaved imitation tasks by controls and infants of diabetic mothers (IDM).*

on deferred imitation of pairs of actions between the groups was related to a *specific* prenatal risk, correlation analyses were conducted using newborn ferritin concentrations as a measure of prenatal iron deficiency and birthweight *z*-scores as a measure of hypoxia and/or hyperinsulemia. Although birthweight *z*-scores were not related to deferred recall ($p>0.90$), newborn ferritin concentration was marginally related to performance on delayed recall of actions in the correct temporal order: $r(27)=0.36$, $p=0.07$. Specifically, lower ferritin levels were associated with lower performance on temporally ordered recall in the deferred imitation task. Thus, an infant's iron status at birth, as indexed by ferritin, may address the extent of metabolic irregularity experienced prenatally and possible influences on behavioral outcomes one year later.

Discussion

Results of the present investigation indicate that even after differences in gestational age and global cognitive functioning are controlled, IDMs' delayed recall performance is below that of a control group at one year of age. This finding is consistent with the hypothesis that the risk factors accompanying the diabetic pregnancy alter explicit memory performance. Interestingly, this deficit appeared to be specific in that it altered temporally ordered recall only after a delay was imposed. Although IDMs' performance did not differ relative to controls on the immediate imitation and interleaved imitation tasks, and thus initially appeared asymptomatic, when memory demands were imposed by means of a delay, their performance began to decline relative to that of controls.

One experimental factor that may partially account for the differences in recall performance between the two groups was the filled delay, that is, participating in another task while holding the to-be-recalled information in memory. Perhaps it is this additional demand of transferring and holding information in memory while completing another task with different materials that lead to the disparity between the groups: with the IDM group exhibiting more interference and/or forgetting than the control group. Although previous research has indicated that slightly older infants' (aged 20 months) performance on filled and unfilled delays did not differ (Bauer et al. 1999), the relative contributions of the delay itself and the potential interference caused by intervening events could not be disentangled in the present investigation. However, given the absence of effects for the interleaved task, there is at present no evidence to suggest that this factor accounts solely for differences in performance.

It is important to note that these behavioral differences were not the result of a pre-existing discrepancy in the nature of the infants' interactions with test materials, due to the fact that the baseline measures did not differ between the groups. Nor can the results be attributed to differences in attention, motivation, or understanding of the task, as the two groups produced an equal number of target actions and the correct order of those actions when they were allowed to do so immediately after modeling. This effect occurred regardless of whether the presentation was blocked, as in the immediate imitation task, or interleaved. In short, such performance indicates that infants in the two groups were equally engaged in the tasks and that they were willing and able to participate.

Results from this investigation are consistent with previous reports on older IDMs who present with poor cognitive outcomes on measures of general cognitive ability when they reach school age (Rizzo et al. 1997, Tamura et al. 2002). The present study utilized an assessment that had greater neural specificity than conventional developmental outcome measures, and controlled for variability in both general cognitive abilities and gestational age in order to investigate specific deficits in explicit mnemonic performance. Results suggest that deficits in explicit memory performance could not be solely attributable to differences in gestational age or general cognitive abilities. Furthermore, given that these measures were obtained at one year of age (rather than at later years) and that the infants were iron deficient in the pre- but not postnatal period (Georgieff et al. 2002), hypotheses regarding connections between prenatal experiences and behavioral outcome are more robust.

The marginal association between newborn ferritin concentration and behavioral recall on the delayed memory task suggests that prenatal iron status may be an important risk factor associated with cognitive outcome in diabetic pregnancy. Animal models of prenatal iron deficiency suggest that this difference in performance may be a result of alterations in brain development during the prenatal period. It is presumed that the hippocampus transfers encoded information from short-term storage to a more permanent state for successful completion of the deferred imitation task. Results of both animal and human research suggest that IDMs incur damage to this region (Petry et al. 1992; Rao et al. 1999, 2003; Jorgenson et al. 2003). Specifically, animal models have indicated that low levels of brain iron influence enzyme systems regulating brain growth, myelination, dopamine receptor synthesis, and energy metabolism, which may lead to adverse neurocognitive and behavioral sequelae (de Ungria et al. 2000, Lozoff 2000, Beard 2003). Several investigations have suggested a selective influence of iron deficiency on neuronal energy metabolism in regions of the hippocampus and in the prefrontal cortex (de Ungria et al. 2000, Rao et al. 2003), both of which are regions associated with explicit memory performance. Taken together, these studies suggest a relation between prenatal iron deficiency due to maternal diabetes and deficits in explicit memory performance.

In conclusion, the results of the present investigation are consistent with the hypothesis that risk factors associated with diabetic pregnancy alter prenatal development, which can influence memory performance on a delay recall task. Future investigations should attempt to further isolate contributions of the independent risk factors (e.g. prenatal iron deficiency) and their combined influence to illuminate their impact on neurobehavioral outcomes and explore their influence across the life span.

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List of abbreviations

IDM	Infants of diabetic mothers
MDI	Mental development index
PDI	Psychomotor developmental index