# DECLARATIVE MEMORY PERFORMANCE IN INFANTS OF DIABETIC MOTHERS

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## I. Introduction

Converging evidence from multiple lines of research has implicated medial temporal lobe (MTL) structures, including the hippocampus, in the conscious recollection of facts and events (i.e., declarative memory; Squire, 1992; see Chapter 1). Some of the most compelling support for this association comes from studies in adults showing that discrete lesions to the hippocampus and surrounding MTL regions result in profound deficits in memory performance (e.g., Mishkin & Appenzeller, 1987; Scoville & Milner, 1957). Fortunately, isolated lesions to these regions are not common in human infants. Nevertheless, the prolonged immaturity of these



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structures during the perinatal period makes them vulnerable to abnormalities in the fetal environment (see Bachevalier, 2001 and Seress, 2001 for review of hippocampal development in nonhuman and human primates, respectively). Following this line of reasoning, it is hypothesized that infants whose brains develop in an abnormal prenatal milieu may experience perturbations in the development of these neural structures, which could ultimately result in impairments in memory ability later in life. One example of such an abnormal prenatal environment is the one that accompanies the diabetic pregnancy.

In the United States, approximately 3–10% of pregnancies are complicated by abnormal glycemic control (Nold & Georgieff, 2004; US Food & Drug Administration, 2004). Of these, 80% are caused by gestational (as opposed to pregestational) diabetes mellitus, a figure that is expected to rise significantly in coming years as the current overweight pediatric population enters into their child-bearing years (Nold & Georgieff, 2004). The prenatal environment that accompanies the diabetic pregnancy is characterized by several chronic metabolic insults that can affect fetal brain health, including hyperglycemia, iron deficiency, and hypoxemia (i.e., insufficient oxygenation of the blood). Clinical conditions resulting from multiple metabolic abnormalities are rarely pure events and in fact multiple pathways exist through which maternal diabetes results in alterations to the general fetal metabolic milieu. One such pathway is as follows: pregnancy increases insulin requirements due to the increased production of hormones. In up to 10% of women, this increased insulin need is not met, resulting in "gestational diabetes" characterized by maternal hyperglycemia (i.e., high levels of glucose in the expectant mother's blood). This excess glucose passes easily through the placenta and causes the fetus to become hyperglycemic as well. Hyperglycemia can cause the fetus to become chronically hypoxemic (or oxygen deficient in the blood), which can stimulate available fetal iron to be shunted away from the brain and into the red blood cells (to compensate for the low oxygen environment; Georgieff *et al*., 1990; Georgieff, Schmidt, Mills, Radmer, & Widness, 1992). In addition, hyperglycemia can result in the fetus releasing its own insulin, which in turn may drive the fetal blood sugar to abnormally low values, particularly if the mother's blood sugar is rapidly lowered. Thus, through this and other pathways, gestational diabetes may result in fetal hyperglycemia/hypoglycemia, chronic hypoxemia, and iron deficiency (see Nold & Georgieff, 2004, for a comprehensive review).

Each of these chronic metabolic abnormalities has been shown to be a risk factor for the developing brain (e.g., Beard, 2008; Hawdon, 1999; Lozoff & Georgieff, 2006; Malone, Hanna, & Saporta, 2006; Malone *et al*., 2008; Rao *et al*., in press; Volpe, 2001; Widness *et al*., 1981). Their

combined and cascading effects during the diabetic pregnancy have been shown to alter fetal and postnatal physical development (as reflected by increased rates of macrosomia or large birth weight), motor development (as reflected by increased jitteriness, lethargy, and movement disorders), and cognitive development. For example, early reports on the cognitive outcome of infants of diabetic mothers (IDMs) by Rizzo and colleagues (Rizzo, Metzger, Burns, & Burns, 1991; Rizzo, Metzger, Dooley, & Cho, 1997) documented an inverse correlation between maternal lipid and glucose metabolism measures obtained late in the diabetic pregnancy and IQ scores as well as measures of cognitive functioning in middle to late childhood. Moreover, these findings suggested that the severity of diabetes during pregnancy was directly related to long-term cognitive risk: the more unregulated the diabetic condition the worse the cognitive outcomes. More recent data have also suggested that the diabetic pregnancy increases risk for major disorders of cognition, such as schizophrenia, up to sevenfold in children (Cannon, Jones, & Murray, 2002; Van Lieshout & Voruganti, 2008). These findings not only highlight the severity of outcomes that are associated with the diabetic pregnancy, but also their persistent effects throughout the lifespan.

Severity of diabetes during pregnancy is tightly linked with the severity of the metabolic risk factors described above (fetal iron deficiency, hypoxemia, and glucose abnormalities). Therefore, the specific effects of each factor on neurologic development are difficult to tease apart in human studies of maternal diabetes. Yet, because effects do differ, it is reasonable to suggest that certain cognitive deficits observed in IDMs (e.g., cognitive impairment) are due to alterations in specific brain regions (e.g., hippocampus) brought about by particular abnormalities in the fetal environment (e.g., iron deficiency). For example, Tamura *et al.* (2002) have shown that impairments in cognitive performance is driven by fetal iron deficiency, as newborn measures of reduced fetal iron stores are associated with diminished IQ scores at school age (cf. Lucas, Morley, & Cole, 1988; Stevens, Raz, & Sander, 1999). Similarly, in a recent large cohort study, maternal iron deficiency during gestation was associated with increased risk of schizophrenia in offspring in a dose-dependent manner (Insel, Schaefer, McKeague, Susser, & Brown, 2008).

Due to enhanced experimental control, data from rodent models have been more successful in linking individual risk factors with specific outcomes. As mentioned above, the hippocampus and surrounding regions exhibit protracted development during the prenatal period; thus, this region may be especially vulnerable to disruption during development. Data from rodents (Carlson *et al.*, 2009; de Ungria *et al.*, 2000; Jorgenson, Wobken, & Georgieff, 2003; Rao, Tkac, Townsend, Gruetter, &

Georgieff, 2003) support this argument and indicate that prenatal iron deficiency *selectively* damages the hippocampal structure (in the areas of the dentate gyrus, CA1 and CA3c) and alters cellular processes as well (e.g., long-term potentiation from CA1: see Jorgenson, Wobken, & Georgieff, 2004). It also suppresses the expression of brain-derived neurotrophic factor (BDNF) not only during the period of iron deficiency but also in adulthood, long after complete iron repletion (Tran, Carlson, Fretham, & Georgieff, 2008; Tran, Fretham, Carlson, & Georgieff, 2009). BDNF is critical for the neural proliferation, differentiation, and synaptic plasticity in the hippocampus. Iron deficiency also significantly alters gene expression, particularly of those genes involved in synaptogenesis and dendritic structure during the period of hippocampal differentiation and in adulthood (Carlson, Stead, Neal, Petryk, & Georgieff, 2007). Finally, the effects of prenatal iron deficiency have been observed at the behavioral level on tasks known to be mediated by the hippocampus (e.g., swim distance on the Morris water maze and radial arm maze behavior; Felt & Lozoff, 1996; Schmidt, Waldow, Salinas, & Georgieff, 2004, respectively).

These effects of iron deficiency are exacerbated if the animal is also hypoxemic (Rao *et al.*, 1999), which is the case in the intrauterine environment of IDMs. Hypoxic–ischemic events that arise early in development have been shown to independently alter metabolic activity in the hippocampus (using cytochrome oxidase; Nelson & Silverstein, 1994) and the distribution of iron-binding protein (ferritin), ultimately delaying the appearance of myelin in the brain (Cheepsunthorn, Palmer, Menzies, Roberts, & Connor, 2001; see also Nyakas, Buwalda, & Luiten, 1996). Hypoglycemia has been found to alter the hippocampus in the perinatal rat pup (e.g., Barks, Sun, Malinak, & Silverstein, 1995) with rapidly proliferating areas being particularly at risk (i.e., CA1, and LTP, in the perinate and the dentate gyrus in the adult, see Yamada *et al.*, 2004). Thus, the protracted and complex development of the hippocampus may make it a primary target for metabolically based disruption of structure and function in IDMs.

In summary, due to the fact that the hippocampus is (a) necessary for memory performance, and (b) may be selectively at risk for perturbations in development when exposed to the abnormal prenatal environment that characterizes the diabetic pregnancy, we hypothesized that IDMs would show deficits in performance on declarative memory tasks that cannot be accounted for by general cognitive impairments. To explore this hypothesis, in our investigation we utilized two measures of memory: (a) recall as measured by behavioral imitation in the elicited/deferred

imitation paradigm, and (b) recognition as measured by electrophysiological responses recorded at the scalp to familiar and novel stimuli.

The data for this report are from an ongoing longitudinal investigation examining the long-term impact of the abnormal prenatal environment experienced by IDMs on the developing brain and memory performance (see DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005; deRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000; Georgieff, Wewerka, Nelson, & deRegnier, 2002; Nelson *et al*., 2000; Nelson, Wewerka, Borscheid, deRegnier, & Georgieff, 2003; Riggins, Miller, Bauer, Georgieff, & Nelson, 2009a for previous reports on this sample). We present data from infants at 12 and 24 months of age. At both assessments, the IDM and control groups participated in three imitation tasks measuring declarative memory via behavior (i.e., immediate recall, 10-min delayed recall, and interleaved presentation). After a 1-week delay, participants returned to the laboratory and measures of recognition memory for one familiar sequence and one novel sequence were recorded via infants' electrophysiological responses to pictures of these stimuli (i.e., event-related potentials or ERPs).

Previous research utilizing ERPs has defined two components in the electrophysiological response that reflect aspects of long-term visual recognition memory (Bauer *et al*., 2006; Bauer, Wiebe, Carver, Waters, & Nelson, 2003; Carver, Bauer, & Nelson, 2000; Lukowski *et al*., 2005). These components have been shown to correlate with behavioral recall in both younger infants and older children (Bauer *et al*., 2003, 2006; Carver *et al*., 2000; Riggins, Miller, Bauer, Georgieff, & Nelson, 2009b). The first component (referred to as the Nc) is a deflection in the waveform that occurs approximately 400–800 ms after stimulus onset (Courchesne, Ganz, & Norcia, 1981; Nelson, 1994). Typically, this deflection is maximally negative at frontal and central midline leads and thus has been termed the "negative central component" or "Nc" (Nelson, 1994). Reports suggest that when using an average reference this deflection appears positive at lateral-posterior sites, although it has not yet been established whether this activity originates in the same cortical areas as the anterior-based Nc (Bauer *et al*., 2006; Lukowski *et al*., 2005). The Nc is thought to reflect attentional processes that are modulated by memory (Carver *et al*., 2000; Courchesne *et al*., 1981; de Haan & Nelson, 1997; Nelson, 1994; Nelson, Henschel, & Collins, 1993; Richards, 2003) and originate in regions in the frontal cortex (e.g., the anterior cingulate; Reynolds & Richards, 2005), with larger deflections indicating greater allocation of attention (Nelson *et al*., 1993). The Nc is typically followed by slow wave activity, which is the second component of interest. This component is represented by a diffuse deflection in the waveform following the

presentation of an event or stimulus, and is thought to reflect continued cognitive processing of the stimulus (e.g., memory updating; de Haan & Nelson, 1997; see also de Haan, 2007; DeBoer *et al.*, 2005 for further discussion).

The combined use of behavioral assessments of recall (via elicited or deferred imitation paradigms) and electrophysiological assessments of recognition memory (via ERPs) allows for a unique glimpse into the processes underlying memory performance in preverbal infants and children. Whereas the elicited imitation paradigm allows for an assessment of behavioral recall (Bauer & Mandler, 1992), ERPs allow for recording of the spatiotemporal distribution of neural events during stimulus processing (i.e., recognition memory; DeBoer *et al.*, 2005; Nelson & Monk, 2001). Thus, the fusion of these two techniques begins to address the neurological underpinnings of memory development that are grounded in observable behavior. This methodological approach was utilized in the present report to explore whether, relative to a control group, IDMs' declarative memory abilities are impaired in the first and second years of life.

## II. Method

### A. PARTICIPANTS

Pregnant women were recruited at approximately 28 weeks gestation from hospitals in Minneapolis/St. Paul metropolitan region. Infants delivered at 32 weeks gestation or greater (as determined by maternal dates or by first trimester ultrasound) and who had a 5-min Apgar scores equal to or greater than 6 were included. At the time of delivery, infants were assessed for signs of iron deficiency via cord serum ferritin concentrations and exposure to hypoxemia and hyperinsulinemia via neonatal macrosomia.[1] Infants with ferritin levels less than 76 μg/L were considered iron deficient during the fetal period (Tamura *et al.*, 2002), infants with levels less than 35 μg/L were considered deficient in brain iron stores during the fetal period (Siddappa *et al.*, 2004), and infants whose birth weight *z*-scores were greater than 2 standard deviations above the population mean were considered at risk for chronic fetal hypoxemia and hyperinsulinemia.

[1]Since red blood cell counts are directly correlated with lack of maternal glycemic control and size for dates in both IDM and non-IDM infants, birth weight *z*-scores were used as a separate index of fetal risk exposure (see Akin *et al.*, 2002; Green *et al.*, 1992; Morris *et al.*, 1985).

The sample reported on in this chapter consists of 70 infants (51 controls [26 female] and 19 IDMs [11 female]) of which 1% were Asian American, 4% were African American, 3% were Hispanic or Latino, and 91% were Caucasian. Due to the overlap between participants tested at both 12 and 24 months (i.e., 38 children, or 54%, contributed data at both sessions), group characteristics are presented for the entire sample, followed by empirical data from each age group (see summary in Table I).

*1. Gestational Age*

Each infant was delivered at 32 weeks gestation or more; however, there were differences between gestational ages in the final sample reported in this publication. On average, infants in the IDM group were born earlier ($M = 38$, SD $= 2$ weeks) than infants in the control group ($M = 39$, SD $= 1$ week), $F(1, 68) = 11.73$, $p < .01$. Given that optimal management of the diabetic pregnancy is to deliver between 37 and 38 weeks due to the increased risk of fetal death late in gestation (i.e., after 38 weeks; Lucas, 2001; Nold & Georgieff, 2004), this difference is not surprising. However, because performance on the elicited imitation task may vary as a function of premature birth (e.g., 27–34 weeks; see Chapter 5; de Haan, Bauer, Georgieff, & Nelson, 2000), gestational age was entered as a covariate in all analyses of elicited and deferred imitation performance in an attempt to statistically control for these effects.

*2. Prenatal Iron Status*

Immediately following delivery, cord blood serum was obtained, centrifuged, and frozen at $-80\,^{\circ}$C until assayed for ferritin concentration. To determine if the two groups (control group $n = 40$, IDM group $n = 18$) were different in iron status at birth, a one-way analysis of variance (ANOVA) was computed on newborn serum ferritin levels with group (IDM, control) as the between-subjects factor. There were no differences between the control ($M = 140$, SD $= 82$) and IDM ($M = 104$, SD $= 114$) groups' newborn mean ferritin levels ($p = .18$). However, 50% (9/18) of the infants in the IDM group had newborn ferritin levels $\leq 76$ μg/L compared to 20% (9/40) of infants in the control group; thus, significantly more infants in the IDM group were considered "iron deficient" than controls in the prenatal period, $\chi^2(1, N = 58) = 5.39$, $p < .05$. In addition, 44% (8/18) of the infants in the IDM group had newborn ferritin concentrations $\leq 35$ μg/L compared to only 5% (2/40) of infants in the control group; thus, more infants in the IDM group experienced "brain iron deficiency" compared to controls, $\chi^2(1, N = 58) = 13.54$, $p < .001$.

Table I
Summary of Group Characteristics for the Control and IDM Groups

| | Control | | | IDM | | | |
|---|---|---|---|---|---|---|---|
| | *M* | SD | *n* | *M* | SD | *n* | Statistics |
| Gestational age (weeks) | 39 | 1 | 51 | 38 | 2 | 19 | $F(1, 68) = 11.73$, $p < .01$ |
| Birth weight (g) | 3587.67 | 493.41 | 51 | 3757.67 | 863.84 | 19 | ns |
| Birth weight $z$-score | .56 | .97 | 51 | 1.85 | 2.07 | 19 | $F(1, 68) = 12.76$, $p < .01$ |
| Macrosomic (bw $z$-score $> 2$) | 8% (4/51) | | | 47% (9/19) | | | $\chi^2(1, N = 70) = 14.30$, $p < .001$ |
| Newborn ferritin (μg/L) | 140 | 82 | 40 | 104 | 114 | 18 | ns |
| Iron deficient <76 μg/L | 20% (8/40) | | | 50% (9/18) | | | $\chi^2(1, N = 58) = 5.39$, $p < .05$ |
| Brain iron deficient <35 μg/L | 5% (2/40) | | | 44% (8/18) | | | $\chi^2(1, N = 58) = 13.54$, $p < .001$ |
| Postnatal ferritin (μg/L) | 55 | 36.04 | 11 | 47.8 | 25.48 | 5 | ns |
| 12 Month MDI | 103 | 9 | 49 | 96 | 8 | 17 | $F(1, 64) = 6.37$, $p < .05$ |
| 12 Month PDI | 100 | 15 | 49 | 95 | 18 | 16 | ns |
| 30 Month MDI | 102 | 12 | 44 | 93 | 13 | 11 | $F(1, 53) = 4.41$, $p < .05$ |
| 30 Month PDI | 98 | 12 | 43 | 92 | 15 | 11 | ns |
| Age at 12 month EI (days) | 369 | 11 | 29 | 371 | 12 | 14 | ns |
| Age at 24 month EI (days) | 726 | 14 | 50 | 731 | 14 | 15 | ns |

ns = not significant, MDI = Bayley Scales of Infant Development, Mental Developmental Index, PDI = Bayley Scales of Infant Development, Physical Developmental Index, EI = Elicited Imitation assessment.

*3. Postnatal Assessments*

In order to determine whether the low iron status was pervasive across the first year of life, a follow-up measure of iron status was also obtained between 6- and 12-months of age by the infant's primary care provider. Eleven of the control participants ($M = 55$ μg/L, SD = 36 μg/L) and 5 of the IDM participants ($M = 48$ μg/L, SD = 26 μg/L) contributed data for this measure. At the postnatal follow-up assessment, iron status did not differ between the groups ($p = .70$). All infants, regardless of group status, had ferritin concentrations within the normal range (range 21–143 μg/L). Thus, if iron deficiency occurred prenatally, it was resolved by the end of the first year of life. This finding of postnatal iron sufficiency following prenatal iron deficiency due to experience of a diabetic fetal milieu is consistent with the follow-up of newborn iron deficiency reported for the larger longitudinal group from which this subsample was derived (Georgieff *et al.*, 2002), and suggests that any differences found in the current investigation related to iron status are not due to ongoing nutrient deficits during the postnatal period, but rather are residua of previous deficits.

*4. Prenatal Hypoxemia, Hyperglycemia, and Reactive Hypoglycemia*

To determine if the two groups differed in weight at birth, a one-way ANOVA with group (IDM, control) as the between-subjects factor was computed on birth weight *z*-scores. The IDM group's mean standardized birth weight score ($M = 1.85$, SD = 2.07) was significantly greater than that of the control group ($M = .56$, SD = .97, $F(1, 68) = 12.76$, $p < .01$). Whereas only 8% (4/51) of the control participants had a birth weight *z*-score greater than 2 standard deviations above the population mean, 47% (9/19) of the infants in the IDM group had birth weight *z*-scores greater than 2 standard deviations above the mean. Therefore infants in the IDM group were suspected to have experienced risk factors such as hypoxemia (Akin *et al.*, 2002; Georgieff *et al.*, 1990; Green, Khoury, & Mimouni, 1992; Morris, Grandis, & Litton, 1985) or hyperinsulinemia (Schwartz & Teramo, 2000) significantly more often than controls during the prenatal period, $\chi^2(1, N = 70) = 14.30$, $p < .001$.

*5. Summary of Sample Characteristics*

In sum, although the IDM group as a whole was exposed to greater risk prenatally than the control group (as indexed by neonatal serum ferritin concentrations and macrosomia), these risk factors did not always apply at the level of the individual. Diabetes during gestation is a highly variable condition and the sample included in the present report reflects the wide

spectrum of disease severity commonly found in maternal–infant pairs. Therefore, estimates of group differences in our sample will be conservative due to the heterogeneous risk profile of the IDM group. Given that our sample accurately reflects variability in the population, the current report is well suited to address the impact of the average range of metabolic fetal milieu associated with the diabetic pregnancy and our findings can be generalized to the greater population.

## B. ASSESSMENTS

### *1. Bayley Scales of Infant Development*

The Bayley Scales of Infant Development, second edition (BSID-II), were administered at 12 months ($n = 66$; $M = 12$ months, 4 days, SD = 42 days) and/or 30 months of age ($n = 55$; $M = 30$ months, 10 days, SD = 17 days). There were no differences between the groups at the age of test ($p$s $> .25$).

To investigate possible group differences in general cognitive functioning, two separate univariate ANOVAs were conducted on the mental development index (MDI) and physical development index (PDI) scores for both the 12- and 30-month assessments. Although the PDI did not differ between the groups at 12 or 30 months of age ($p = .26$ and .13, respectively), the MDI score, which is thought to index general cognitive abilities, did differ between the two groups at both 12 and 30 months of age. At 12 months of age, although both the control and IDM group's mean score fell well within the bounds of the population standard norms ($100 \pm 15$), the control group's score ($M = 103$, SD = 9) was significantly greater than that of the IDM group ($M = 96$, SD = 8), $F(1, 64) = 6.37$, $p < .05$. Similarly, at 30 months of age, both groups' mean MDI score was within the normal range, yet the control group's score ($M = 102$, SD = 12) was significantly greater than that of the IDMs ($M = 93$, SD = 13), $F(1, 53) = 4.41$, $p < .05$.

### *2. 12-Month-Old Imitation*

A total of 43 infants (29 control, 14 IDM) participated at the 12-month assessment. For the declarative memory tasks: 41 infants (28 control, 13 IDM) contributed data to the immediate recall task, 39 infants (27 control, 12 IDM) contributed data to the 10-min delayed recall task, and 41 infants contributed data to the interleaved presentation task (27 controls, 14 IDMs). Missing data were attributable to video equipment failure ($n = 2$) and experimenter error ($n = 2$). Mean corrected age (i.e., based on due date) at the first testing session was approximately 12 months

(370 ± 11 days; range 350–398); there were no differences between the groups in age at time of test ($p = .64$).

After a 1-week delay ($M = 7$ days, SD = 1), infants returned to the laboratory for the electrophysiological recording. There were no differences between the groups in length of delay ($p = .71$). A total of 14 infants (7 control, 7 IDM) provided artifact-free data at the 12-month ERP session; reasons for missing data were refusal to wear the cap ($n = 4$), too few artifact-free trials ($n = 23$), or families missed the session ($n = 2$). Such attrition is consistent with previous reports of ERP research with infants (e.g., Nelson *et al.*, 1993, see also DeBoer *et al.*, 2005) and no differences were suspected between infants who provided artifact-free data and infants who did not (see Gunnar & Nelson, 1994).

*3. 24-Month-Old Imitation*

A total of 65 children (50 control, 15 IDM) participated at the 24-month assessment. For the declarative memory tasks: 59 children (44 controls, 15 IDMs) contributed data to the immediate and 10-min delayed recall tasks, and 58 children contributed data to the interleaved presentation task (43 controls, 15 IDMs). Missing data ($n = 6$) were again attributable to random factors unrelated to group characteristics. The mean corrected age at the first testing session was 24 months ($M = 24$ months, 7 days, SD = 14 days; range 23 months 11 days–25 months 15 days); there were no differences in age at test between the groups ($p = .30$).

After a 1-week delay ($M = 7$, SD = 1), children returned to the laboratory for the electrophysiological recording. There were no differences between the groups in length of delay ($p = .63$). A total of 17 children (9 control, 8 IDM) provided artifact-free data at the 24-month ERP session; reasons for missing data were refusal to wear the cap ($n = 9$), too few artifact-free trials ($n = 25$), unacceptable reference recording ($n = 4$), or artifact contaminated data due to excessive eye and/or muscle movement ($n = 10$).

*4. Longitudinal Sample*

A total of 38 participants (28 controls [16 female], 10 IDMs [6 female]) contributed data at both the 12- and 24-month sessions. Infants did not contribute data to the 12-month session due to the following circumstances: funding not being available at time of test ($n = 23$), families missed the session ($n = 2$), or data were yet not available for analysis at the time of this report ($n = 2$). Participants did not contribute data to the 24-month session because families missed the session ($n = 1$), dropped out of the study ($n = 3$), or the infants were too young for the assessment at the time of this report ($n = 1$).

## C. MATERIALS

Each event sequence consisted of target actions (two actions for 12 month olds, four actions for 24 month olds) that produced an interesting and desirable end state (e.g., turning on a light; see Appendix and Bauer, Wenner, Dropik, & Wewerka, 2000; Carver & Bauer, 1999, 2001 for examples). Event sequences for each participant were randomly selected from an existing pool containing 11 different two-step event sequences and eight different four-step event sequences (see Appendix). All events were constrained by enabling relations. The event sequences were counterbalanced across tasks and participants; thus, in the final sample each sequence occurred with equal probability in each task.

Stimuli used during ERP testing were digitized pictures of each target action of the old/familiar event (i.e., one event sequence from the elicited imitation observed at the first laboratory session 1-week prior) and a new event (i.e., one sequence the infant had not seen previously). In addition, pictures of the end state of the correctly completed actions were also shown for the two-step events. The sequences were counterbalanced across participants; thus, each sequence had equal probability of being seen as the familiar and novel stimuli across the participants.

## D. DESIGN AND PROCEDURE

At both the 12- and 24-month sessions, participants visited the laboratory for three testing sessions that lasted approximately 1 h each. The first session consisted of a warm-up period followed by the imitation paradigm during which measures of immediate recall, 10-min delayed recall, and interleaved presentation performance were obtained. In the immediate and 10-min delayed recall tasks a baseline phase was completed, then the target actions (accompanied by verbal labels) for a given event sequence were modeled two times in immediate succession and infants are allowed to imitate (either immediately or after a delay[2]). Alternatively, in the interleaved presentation version of the task, the target actions (and verbal labels) of one event sequence were presented

[2]The delay period of the deferred imitation task was "filled;" that is, during the delay infants participated in the baseline and imitation phases of the immediate imitation task. A filled delay was used for two reasons: first, it mimics real world experience where intervening events between encoding and retrieval are quite common and second, previous research has suggested performance on tasks with filled and unfilled delays does not differ significantly (Bauer, Van Abbema, & de Haan, 1999).

interspersed with steps from another event sequence. After this interleaved demonstration of both sequences, the infants were given the props for each sequence for imitation in turn (see Bauer, 2004; Bauer & Starr, 2003 for further elaboration). Performance on two different sequences was recorded for each of the three tasks and averaged together in order to obtain the dependent measure of recall.

As in previous research, the baseline phase served as a control for general problem solving skills or fortuitous production of the event sequences (e.g., Bauer *et al*., 2000). No baseline measure was used in the interleaved task due to the fact it is an analog to a working memory task and the cognitive processes of interest were the binding and integration of the information over time (Bauer, 2004). If the elements of the sequence had been presented in advance of modeling, one could not have been certain that the processes were carried out during modeling. Therefore, baseline measures from the immediate and 10-min delayed recall tasks were used in lieu of an actual baseline measure with the interleaved sequences. (Specific event sequences for each task were similar in difficulty and counterbalanced across participants; thus, each sequence occurred with equal probability in each task, again validating the use of the baseline measures from four sequences as representative of overall baseline performance.)

After a 1-week delay, infants returned to the laboratory for the electrophysiological recording during which they viewed randomly presented pictures of one familiar and one novel event sequence from the immediate imitation task. Infants wore nylon Electrocaps$^{X©}$ that were held in place via Velcro straps tucked under their chins (Figure 1) and were tested while seated on their caregivers' laps approximately 75 cm from a computer screen in a dimly lit room. The screen was set within a black barrier so that infants could only view a portion of the room during testing. A maximum of 100 trials were presented to the 12-month-old infants and a maximum of 120 trials were presented to the 24 month olds in a fixed random order with each picture occurring an equal number of times during an individual session.

Data were recorded from multiple scalp electrodes (at both ages: Fz, Cz, Pz, F3, F4, F7, F8, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, P3, P4, T3, T4, T5, T6, O1, and O2; at 12 months only: AF3, AF4; at 24-months only: PO3, PO4, PO7, PO8) placed according to the modified international 10–20 system (Jasper, 1958), two electro-ocular electrodes placed in a transverse position above and below the eye, and two mastoid electrodes affixed via foam adhesive pads. Electrodes were filled with a conductive gel and a mildly abrasive cleanser was used to ensure that impedances were generally below 10 k$\Omega$. EEG signals were recorded

*Fig. 1. Example of the EEG recording cap on a 12-month-old infant.*

using a Grass Neurodata Acquisition System with Model 12A5 amplifiers. EEG gain was set at 20,000 and EOG gain was set at 5000. Bandpass filters were set between .1 and 30 Hz and a notch filter was set at 60 Hz. Each trial consisted of a 100 ms baseline followed by stimulus presentation for 500 ms and data were recorded for 1200 ms after the end of the stimulus presentation. Throughout the recording epoch, EEG was sampled every 10 ms (100 Hz) referenced to Cz. The intertrial interval varied randomly between 500 and 1000 ms, including the 100 ms baseline of the following stimulus.

On the third visit to the laboratory (at 12 and/or 30 months of age), participants were administered BSID-II.

One of three experienced researchers conducted each imitation session and one of two researchers with clinical experience conducted each Bayley Scales assessment. Imitation sessions were recorded via videotape and coded offline by experienced coders who were unaware of the hypothesis of the investigation; reliability was established.

## E. SCORING

### *1. Imitation Task Data*

The imitation tasks were scored as described in Chapter 2. Two different dependent measures were derived: (a) the number of individual target

actions produced, and (b) the number of pairs of actions produced in the target order (referred to as ordered recall). For a two-step sequence, the maximum number of target actions was two and maximum number of pairs of target actions in the correct order was one. For a four-step sequence, the maximum number of target actions was four and maximum number of pairs of target actions in the correct order was three. Data were derived by taking the average performance of target actions and pairs of target actions in the correct order on the two different sequences for each task (immediate, 10-min delayed, and interleaved). To facilitate comparisons across age groups proportions are reported.

*2. ERP Data*

The ERP data were rereferenced offline using an average reference technique for the 12-month-old data (following the procedures outlined in Bauer *et al*., 2006) and a mathematically linked mastoid reference for the 24-month data (as outlined in Carver *et al*., 2000).[3] Averages for each condition (familiar/novel) were obtained for each participant, with the constraint that an equal number of trials were included for each condition. Trials were excluded if the EEG signal exceeded analog to digital values ($\pm 150\ \mu V$) in any 100 ms window, or if the EOG signal changed more than $250\ \mu V$ in any 100 ms window. Consistent with previous research, zero bad electrode channels were allowed during the cross-averaging of the 12-month-old data due to use of the average reference (Bauer *et al*., 2006); data were accepted in the 24-month-old group if fewer than 10% of the channels were missing due to artifacts. The averaged waveforms were then visually inspected to exclude data contaminated by EOG or movement artifact. Grand means were created from the uncontaminated data for each group of infants (i.e., control and IDM) for each event type (i.e., familiar and novel). There were no group differences in the number of trials for either the 12-month (control: $M = 18$, SD = 6; IDM: $M = 14$, SD = 8, $p = .34$) or 24-month groups (control: $M = 38$, SD = 13; IDM: $M = 30$, SD = 15, $p = .29$).

[3]Due to an amplifier problem, data were lost that precluded us from using a mastoid reference in the 12-month-old sample. The focus of the present report is on differences between groups within each age group and no between age group comparisons will be made. We are aware of no data that indicate the influence of different reference configurations on Nc and slow wave components examined in this report.

# III. Results

## A. IMITATION

### *1. Baseline Measures at 12 and 24 Months of Age*

To rule out possible influences of general problem solving skills on recall, univariate analyses of covariance (ANCOVAs) were calculated for target actions and pairs of actions in target order at the baseline assessment for both the immediate and 10-min delayed recall tasks with gestational age as the covariate for each age group (see Tables II and III, Panel A for descriptive statistics). No group differences were expected on the baseline measures since baseline measures are thought to index problem solving abilities and not memory processes *per se*. None of the analyses yielded significant main effects, indicating that there were no differences between the groups' performance on target actions or pairs of actions during the baseline phase at either 12 or 24 months of age. Consequently, variation in recall abilities between the groups cannot be solely accounted for by differences in problem solving skills or willingness and ability to interact with the props.

### *2. 12-Month Imitation Data*[4]

Univariate ANCOVAs were calculated for target actions and ordered pairs of actions for the immediate, 10-min delayed, and interleaved presentation tasks with gestational age as a covariate (see Table II for descriptive statistics). Although there were no differences in performance on the immediate or interleaved presentation tasks, there were differences between the two groups' performance on the 10-min delayed recall task. Specifically, there were differences between the groups' recall of individual target actions, $F(1, 36) = 3.26$, $p = .079$, and recall of pairs of target actions in the correct order, $F(1, 36) = 6.59$, $p < .05$. Thus, when a 10-min delay was imposed, the IDM group produced fewer actions and these actions were less well organized compared to the control group.

To address the question as to whether these observed impairments were specific to memory performance or whether they could be accounted for by deficits in general cognitive abilities, we analyzed the data using both gestational age and MDI scores as covariates. When these scores were used to statistically control for differences in general cognitive abilities

[4]Findings for a subset of the sample presented in this chapter can be found in DeBoer, Wewerka, *et al.*, 2005; however, both reports indicate similar results regarding imitation performance.

Table II
Descriptive Statistics of Proportions of Target Actions and Pairs of Actions at Baseline (A) and Recall (B) for Control and IDM Groups at 12 Months of Age

| | | Measure | | | |
|---|---|---|---|---|---|
| | | Target Actions | | Pairs of Actions Ordered Recall | |
| Condition/Group | | Mean | SD | Mean | SD |
| *Panel A: baseline* | | | | | |
| Immediate | Control | .27 | .18 | .04 | .13 |
| | IDM | .31 | .25 | .04 | .14 |
| 10-min Delayed | Control | .31 | .22 | .06 | .16 |
| | IDM | .25 | .27 | .04 | .14 |
| *Panel B: recall* | | | | | |
| Immediate | Control | .68 | .27 | .45 | .34 |
| | IDM | .52 | .33 | .27 | .39 |
| 10-min Delayed | Control | .53† | .29 | .28* | .32 |
| | IDM | .40† | .25 | .08* | .19 |
| Interleaved | Control | .56 | .26 | .24 | .29 |
| | IDM | .48 | .23 | .11 | .21 |

† Denotes $p \leq .10$; * denotes $p \leq .05$.

and gestational age, performance of target actions was no longer different between the two groups ($p = .26$). However, group differences in ordered recall remained marginally lower in the IDM group, $F(1, 34) = 3.86$, $p = .06$. This suggests that impaired recall in the IDM group relative to the control group when a 10-min delay was imposed is not solely attributable to differences in general cognitive abilities or gestational age, but represents a specific deficit in memory (see DeBoer, Wewerka, *et al.*, 2005 for a similar finding).

To explore associations between characteristics of the prenatal environment and differences in behavioral recall, a series of correlational analyses were conducted between perinatal measures (i.e., ferritin, birth weight *z*-scores, gestational age) and the number of pairs of actions recalled after the 10-min delay. Only newborn ferritin levels were related to memory performance: lower iron stores predicted recall of fewer pairs of actions, $r(37) = .27$, $p = .08$.

### *3. 12-Month ERP Data and Relations with Imitation Data*

In this section, results are organized by ERP components of interest (Nc amplitude and latency, followed by slow wave) and discussion of the midline leads precedes that of the lateral leads. To examine the effect of

group on electrophysiological measures of recognition memory at the midline leads, we conducted 2 (group: control, IDM) × 2 (event type: familiar, novel) × 3 (lead: Fz, Cz, Pz) mixed ANOVAs with repeated measures on event type and lead, for each of the three dependent variables: peak amplitude of the Nc, latency to the peak amplitude of the Nc, and area under the curve for slow wave activity. To examine the effects on recognition indices at the lateral leads, we conducted a 2 (group: control, IDM) × 2 (event type: familiar, novel) × 2 (hemisphere: left, right) × 3 (coronal plane: temporal: T5/6, parietal: P3/4, occipital: O1/2) mixed ANOVAs with repeated measures on event type, hemisphere, and coronal plane, for each of the three dependent variables: peak amplitude of the Nc, latency to peak, and area under the curve for the slow wave activity.[5] Greenhouse-Geisser and Bonferroni corrections were used when necessary. Finally, to ground findings from the electrophysiological measures in behavior and relate data from these two different assessment modalities, correlations were conducted between the imitation data (recall of target actions[6]) and the ERP data (i.e., Nc amplitude, latency, and slow wave activity for midline and lateral leads). Significant relations are reported following the discussion of each component.

*4. Nc*

As illustrated in Figures 2 and 3, peak amplitude of the Nc component changed polarity from negative at the anterior and central leads (Fz: $M = -9.29\ \mu V$, Cz: $M = -7.86\ \mu V$) to positive at the posterior lead (Pz: $M = 9.04\ \mu V$), as indicated by a main effect of lead, $F(2, 24) = 31.55$, $p < .001$.

Due to an *a priori* prediction for an effect of condition for the Nc (negative component) at frontal and central midline leads (Carver *et al.*, 2000; Bauer *et al.*, 2003), a separate 2 (group: control, IDM) × 2 (event type: familiar, novel) × 2 (lead: Fz, Cz) repeated measures ANOVAs was conducted. Amplitude to the novel stimulus ($M = -9.96\ \mu V$, SD = 1.37) was slightly greater than to the familiar stimulus ($M = -7.18\ \mu V$, SD = 1.67), $F(1, 12) = 3.10$, $p = .10$. Follow-up analyses using paired samples *t*-tests for both the control and IDM groups indicated that in

[5]Previous research (Stolarova *et al.*, 2003) has shown that brain responses, specifically the topography and the latency of the Nc component, of preterm infants at the age of 6 months are more similar to those of their corrected age peers than to those of the chronological age controls. However, due to the fact that all infants were tested based on their corrected age of 12 or 24 months, gestational age was not covaried in the ERP analyses.

[6]Although ordered recall of target actions (i.e., pairs of actions) was also correlated with the electrophysiological measures, these findings were largely redundant and are not reported due to space limitations.

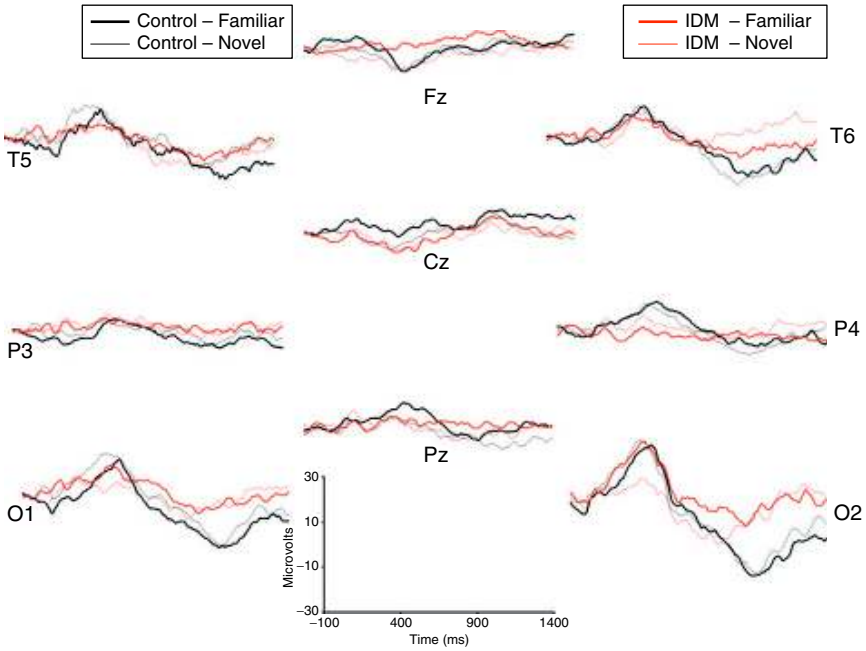


*Fig. 2. Grand averaged ERPs to familiar and novel stimuli for 12-month-old control and IDM groups.*

control group, Nc amplitude was significantly larger to the novel ($M = -9.29\,\mu V$, SD = 4.15) compared to the familiar stimulus ($M = -3.14\,\mu V$, SD = 7.34) at Cz, $t(6) = 2.76$, $p < .05$. However, for the IDM group, Nc amplitude was significantly larger to the novel ($M = -10.86\,\mu V$, SD = 9.84) compared to the familiar stimulus ($M = -4.57\,\mu V$, SD = 5.41) at Fz, $t(6) = 2.46$, $p < .05$; see Figure 3. These results reflect what is observed in the grand means (Figure 2) and suggest that although both groups are discriminating the novel from familiar stimuli, different patterns of activation underlie this ability in the two groups.

Interestingly, only difference scores between Nc amplitude to familiar and novel stimuli at Cz approached significance in predicting performance of target actions at immediate imitation ($r = .52$, $p = .07$); difference scores at Fz did not ($p = .72$). Greater differentiation (or a greater difference score) at Cz was positively related to performance of target actions during the immediate recall task 1-week prior (cf. Bauer *et al.*, 2003).

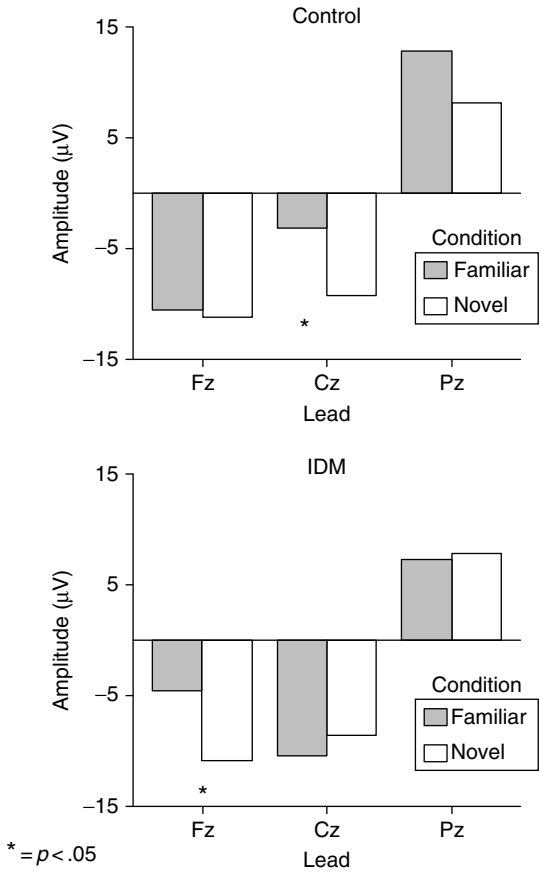


*Fig. 3. Nc amplitude to familiar and novel stimuli for 12-month-old control and IDM groups at midline leads (Fz, Cz, Pz).*

There were no significant effects for latency to peak of the Nc at the midline leads (all $p$s $> .16$) and no relations were found with behavioral recall.

Amplitude of the Nc component at lateral leads differed as a function of location on the scalp, as indicated by a main effect of coronal plane, $F(2, 24) = 9.57$, $p < .01$. Pairwise comparisons suggested that Nc amplitude at temporal ($M = 13.59\,\mu V$, SD $= 5.47$) and occipital ($M = 17.52\,\mu V$, SD $= 9.63$) electrodes was greater than the Nc amplitude at the parietal electrodes ($M = 8.34\,\mu V$, SD $= 6.19$, $p$s $< .05$). Of particular interest, however, was the marginal 3-way group $\times$ condition $\times$ coronal plane interaction, $F(2, 24) = 3.63$, $p = .06$. Follow-up analyses indicated

this interaction was driven by a group × condition interaction at the occipital leads $F(1, 12) = 5.84$, $p < .05$. As illustrated in Figure 4, when follow-up analyses were conducted by group, there was no difference between responses to the familiar and novel stimulus in the control group; however, in the IDM group, the amplitude of the Nc at occipital leads was significantly greater to the familiar stimulus ($M = 18.71$, SD = 8.07) than the novel stimulus ($M = 10.43$, SD = 9.85), $t(6) = 2.72$, $p < .05$. When the

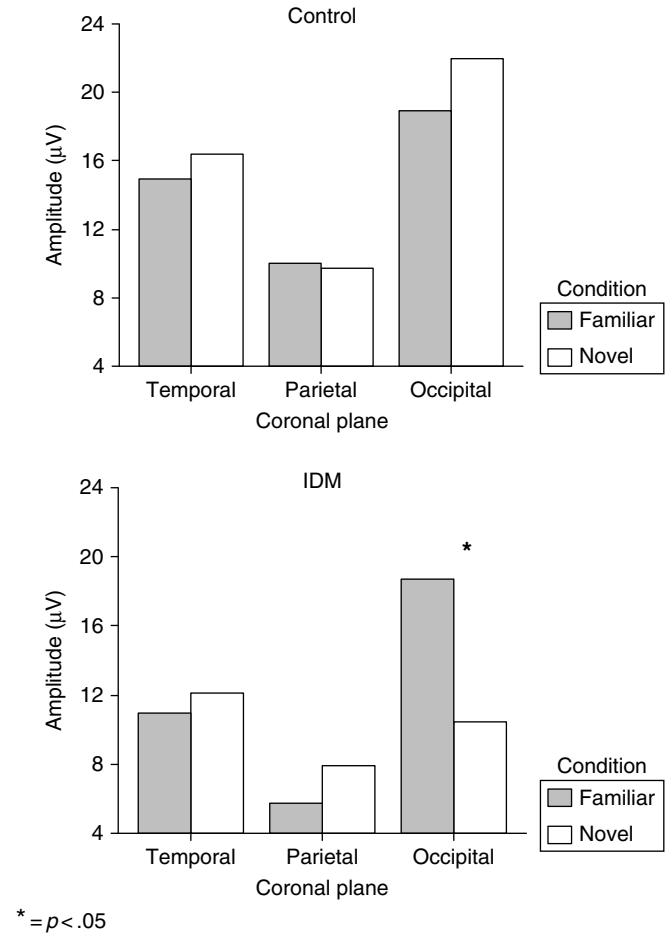


*Fig. 4. Nc amplitude to familiar and novel stimuli in temporal, parietal, and occipital coronal planes for the control and IDM groups at 12 months of age.*

follow-up analyses were conducted by event type, amplitudes to the familiar stimulus did not appear different between the IDM and control groups at the occipital leads; however, peak amplitude to the novel stimulus was significantly greater for the control group ($M = 22.0\ \mu V$, $SD = 11.0\ \mu V$) compared with that of the IDM group ($M = 10.4\ \mu V$, $SD = 9.9\ \mu V$).

Latency to peak for the Nc component at the lateral leads was marginally different as a function of coronal plane, $F(2, 24) = 3.17$, $p = .06$. Pairwise comparisons indicated that regardless of group or event type, latency to peak in the occipital leads ($M = 478.86$ ms, $SD = 68.01$) was significantly faster than latency to peak in the temporal leads ($M = 530.82$ ms, $SD = 66.35$, $p < .05$), and marginally faster than latency to peak in the parietal leads ($M = 523.68$ ms, $SD = 60.70$, $p = .06$).

*5. Slow Wave*

Differential processing of familiar and novel stimuli between groups, as measured by slow wave activity, was not apparent at the midline leads. However, slow wave activity at Cz was correlated with immediate imitation of target actions. Specifically, greater PSW to the familiar stimulus was associated with better performance on the immediate recall task, $r = .58$, $p = .04$ (cf. Riggins *et al.*, 2009b).

Analysis of slow wave activity at the lateral leads suggested a trend toward a main effect of group, $F(1, 12) = 3.65$, $p = .08$. The control group had greater area scores ($M = -5939.6$ ms $\mu V$, $SD = 3852.9$ ms $\mu V$) than the IDM group ($M = -1924.7$ ms $\mu V$, $SD = 4004.2$ ms $\mu V$). This group difference was significant at the occipital leads, $F(1, 12) = 5.18$, $p < .05$, as illustrated in Figure 5. There was also a main effect of coronal plane, $F(2, 24) = 5.56$, $p < .05$. Pairwise comparisons revealed that area scores at the occipital leads ($M = -6870.55$ ms $\mu V$, $SD = 6958.55$) was greater than at the parietal leads ($M = -1068.50$ ms $\mu V$, $SD = 4422.88$). Differences in slow wave activity between familiar and novel stimuli at lateral leads did not correlate with immediate recall performance ($ps > .38$).

*6. 24-Month Recall Data*

As with the 12-month imitation data, univariate ANCOVAs were conducted for target actions and ordered pairs of actions for the immediate, delayed, and interleaved imitation tasks at 24 months of age with gestational age as the covariate (see Table III for descriptive statistics). There were no effects of group on behavioral recall performance (all $ps > .19$).

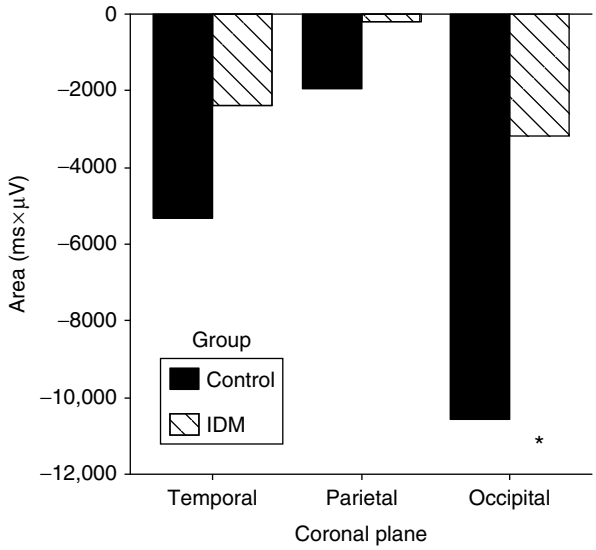


*Fig. 5. Area under the curve in temporal, parietal, and occipital coronal planes for the control and IDM groups at 12 months of age (controls > IDM,* $p < .05$*). * = p < .05.*

Table III
Descriptive Statistics of Proportions of Target Actions and Pairs of Actions at Baseline (A) and Recall (B) for Control and IDM Groups at 24 Months of Age

| | | Measure | | | |
|---|---|---|---|---|---|
| | | Target Actions | | Pairs of Actions Ordered Recall | |
| Condition/Group | | Mean | SD | Mean | SD |
| *Panel A: baseline* | | | | | |
| Immediate | Control | .32 | .14 | .08 | .10 |
| | IDM | .36 | .16 | .14 | .17 |
| 10-min Delayed | Control | .26 | .15 | .07 | .12 |
| | IDM | .32 | .10 | .10 | .08 |
| *Panel B: recall* | | | | | |
| Immediate | Control | .86 | .20 | .71 | .26 |
| | IDM | .85 | .19 | .67 | .24 |
| 10-min Delayed | Control | .83 | .18 | .61 | .28 |
| | IDM | .72 | .27 | .53 | .32 |
| Interleaved | Control | .84 | .19 | .64 | .26 |
| | IDM | .80 | .22 | .56 | .29 |

*7. 24-Month ERP Data and Relations with Imitation Data*

The overall statistical approach followed for the 24-month ERP data is identical to that taken with the 12-month ERP data. However, due to slight differences in data collection for the two age groups, the vertex electrode (Cz) was entered as the lead of interest for the midline analyses and lateral lead analyses were conducted on frontal, parietal, and occipital leads (F7/8, P3/4, O1/2). As before, results involving the Nc component and relations with imitation data are presented followed by results for slow wave activity.

*8. Nc*

At the vertex electrode, there were no significant effects of Nc amplitude or latency. Analyses of the peak amplitude of the Nc at the lateral leads revealed a significant main effect of coronal plane, as a result of a shift in the polarity of the amplitude in this time window, $F(2, 30) = 135.81$, $p < .001$ (see Figures 6 and 7). Pairwise comparisons indicated that amplitude to the Nc at the frontal leads ($M = -17.92$ μV, SD = 8.99) was

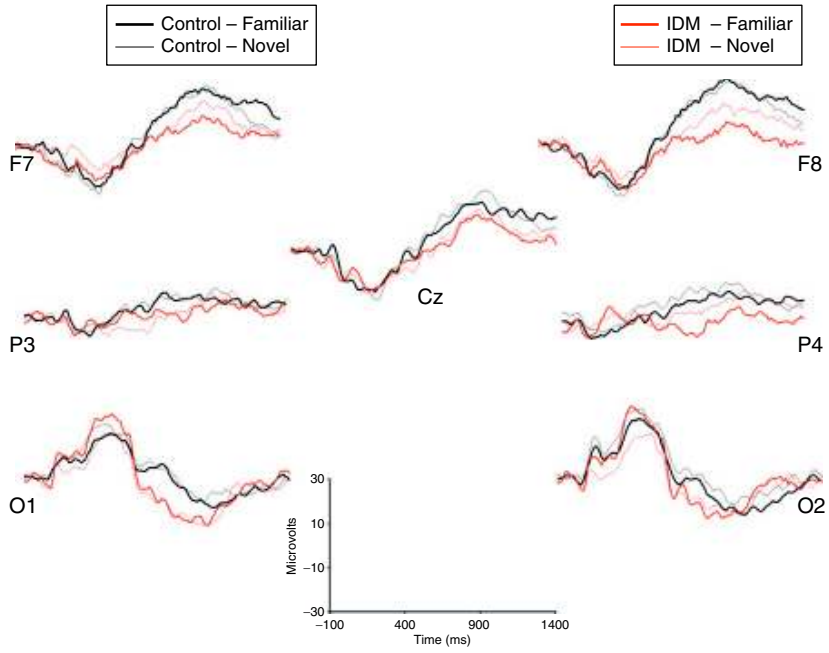


*Fig. 6. Grand averaged ERPs to familiar and novel stimuli for 24-month-old control and IDM groups.*

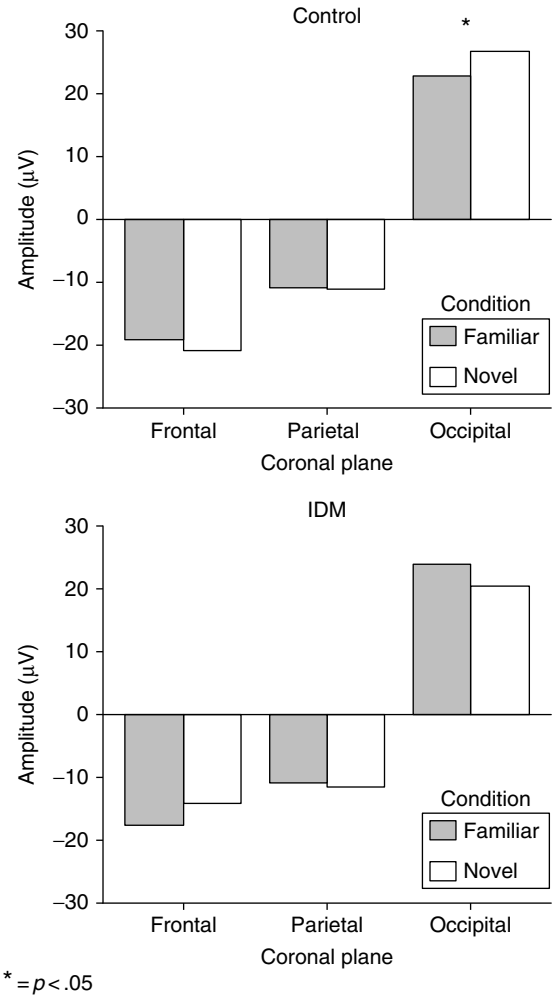


*Fig. 7. Nc amplitude to familiar and novel stimuli in temporal, parietal, and occipital coronal planes for the control and IDM groups at 24 months of age.*

different from that at the parietal leads ($M = -11.08\ \mu V$, SD = 8.19; $p < .05$) and amplitude at both the frontal and parietal leads was different from that at the occipital leads ($M = 23.48\ \mu V$, SD = 12.04; $ps < .001$). Of greater interest, however, was the three-way interaction between group, condition, and coronal plane, $F(2, 30) = 4.04$, $p < .05$. As illustrated in Figure 7, although the IDM group's Nc amplitude was similar for the familiar and novel stimuli over occipital leads ($p = 41$), the control group

had a significantly greater peak to the novel stimulus ($M = 26.72$ μV, SD $= 7.19$) than the familiar stimulus ($M = 22.89$ μV, SD $= 7.35$), $t(8) = 3.13$, $p < .05$.

*9. Slow Wave*

Slow wave activity at the vertex (Cz), regardless of stimulus type, was significantly different between the two groups, $F(1, 15) = 9.34$, $p < .01$. As illustrated in Figure 8, the control group had larger area scores ($M =$ 9811.83 ms μV, SD $= 3568.20$) than the IDM group ($M = 4632.13$ ms μV, SD $= 3392.70$). Similar to results at 12 months of age, at 24 months of age, slow wave activity at Cz to the familiar stimulus predicted immediate imitation of target actions ($r = .49$, $p = .05$; cf. Riggins *et al.*, 2009b). Interestingly, slow wave activity to the familiar stimulus at Cz *also* predicted recall of target actions for the delayed recall task ($r = .51$, $p < .05$) and the interleaved presentation task ($r = .61$, $p < .05$).

Finally, when slow wave activity at the lateral leads was analyzed, main effects of group, $F(1, 15) = 7.00$, $p < .05$, and coronal plane, $F(2, 30) =$ 37.72, $p < .001$ were obtained (see Figure 9). Overall, the control group ($M = 4592.17$ ms μV, SD $= 3614.43$) had larger area scores than the IDM group ($M = -86.51$ ms μV, SD $= 3667.55$). There was also a reversal in polarity of slow wave in this time window: at the frontal ($M =$ 8398.67 ms μV, SD $= 5909.56$) leads there was greater positive slow wave

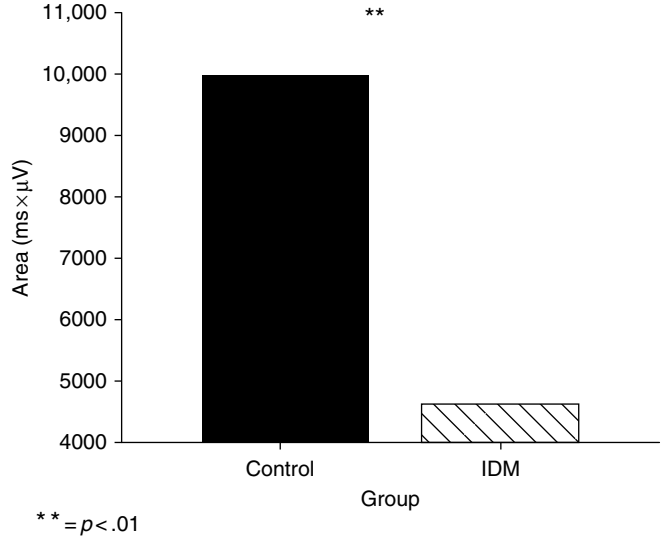


*Fig. 8. Slow wave activity at Cz for the control and IDM groups at 24 months of age.*

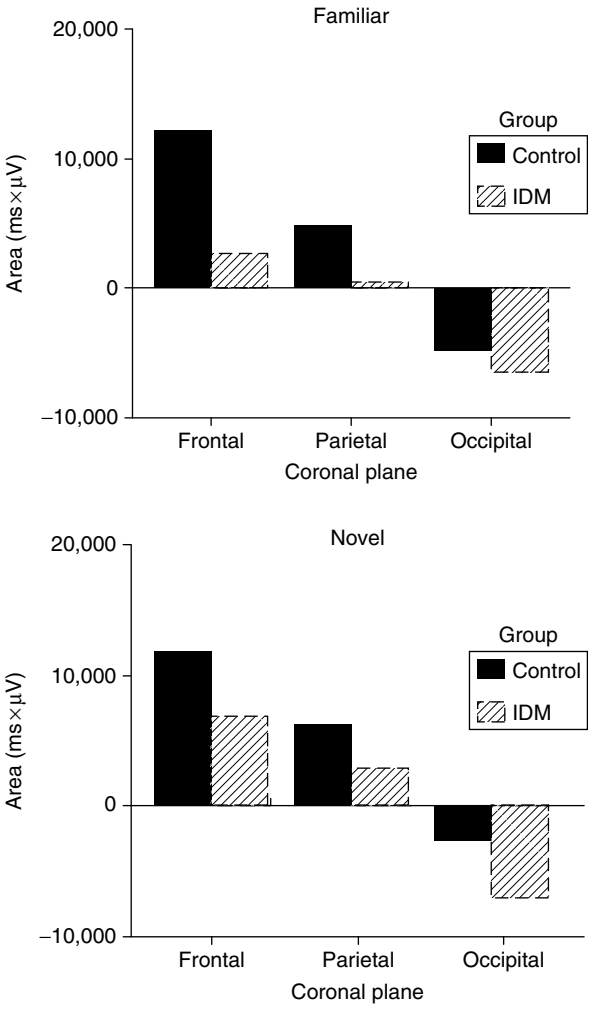


*Fig. 9. Slow wave activity to the familiar and novel stimuli at frontal, parietal, and occipital lateral leads for the 24-month-old control and IDM groups (controls > IDM and frontal > parietal > occipital,* $p < .05$*).*

than at the parietal ($M = 3610.44$ ms μV, SD = 5558.74) leads, and both of these were greater than the negative slow wave activity at the occipital leads ($M = -5250.63$ ms μV, SD = 5645.31; all $p$s $< .05$).

Slow wave activity to the novel stimulus for the lateral leads predicted recall of target actions at the immediate recall task, $r = .62, p < .05$ and recall of target actions for the interleaved presentation task, $r = .60, p < .05$.

## IV. Discussion

At 12 months of age, IDMs differed from the control group on both measures of behavioral recall and electrophysiological indices of recognition memory. Specifically, group differences in behavioral memory measures arose when a 10-min delay was imposed before recall. Group differences in electrophysiological indices of memory arose in measures of Nc amplitude (at midline and lateral occipital leads) and measures of slow wave activity (at lateral leads). Consistent with other reports (e.g., Carver *et al.*, 2000; Lukowski *et al.*, 2005; Riggins *et al.*, 2009b), behavioral recall was related to amplitude of the Nc and slow wave activity to the familiar stimulus. Specifically, the difference in amplitude of the Nc component to the familiar and novel stimuli and slow wave activity to familiar stimuli at Cz was positively related to performance of target actions in the immediate recall task. These findings suggest that associations exist between immediate recall for target actions at Time 1 and (a) allocation of attention to the familiar and novel stimuli 1 week later (i.e., better memory performance at Time 1 was related to greater Nc amplitude differences at Time 2), and (b) memory updating to familiar stimuli (i.e., better memory performance at Time 1 was related to increased slow wave activity at Time 2).

To investigate whether these group differences persist over the first few years of life, we turn to the results from the 24-month age group. At this assessment, group differences in behavioral recall were no longer apparent on the imitation tasks. However, differences in electrophysiological measures of recognition memory remained in Nc amplitude at lateral occipital leads and slow wave activity at both midline and lateral leads. As was the case at 12 months, the number of target actions recalled in the immediate recall task at Time 1 was related to slow wave activity to the familiar stimulus at Cz at Time 2 (i.e., better memory performance at Time 1 predicted increased slow wave activity at Time 2). Thus, although there were no differences in behavioral recall of the event sequences, there were differences in electrophysiological measures of recognition memory.

These findings suggest that when paired with the imitation paradigm, ERPs may provide a sensitive measure that allows for the elucidation of differences in neural correlates of memory processes related to behavioral performance on the task. For example, this methodological combination may begin to reveal details regarding the nature of neural processes contributing to performance on this memory task. At 24 months of age, slow wave activity was not only correlated with measures of immediate recall, but was also correlated with measures of recall on the delayed recall

and interleaved presentation tasks, a finding that may reflect (a) general development of the memory network, (b) changes in task demands that are not observable in behavior, or (c) a combination of the two. Although this is a question that deserves more research, there is some evidence to suggest that brain development is responsible for changes in relations between behavioral recall and electrophysiological responses (Bauer, 2006).

It is possible that variations in developmental trajectories may account for some of the observed differences between the IDM and control groups. At 12 months of age, the control group did not show evidence of differentiation between the novel and familiar stimuli at the occipital leads; however, at 24 months, the control group did show evidence of differentiation between the two classes of stimuli. Conversely, at 12 months, the IDM group did show evidence of differentiation between the familiar and novel stimuli at the occipital leads; however, the effect was in the *opposite* direction: amplitude was greater to the familiar as opposed to the novel stimulus. At the 24-month assessment, this difference disappeared and the ERP responses for the IDM group were similar to the familiar and novel stimuli. One possible interpretation: if we assume data from the control group at 12 and 24 months represent the typical developmental profile, the IDM group is following a delayed developmental trajectory (i.e., if there is a normative developmental shift from greater amplitude to familiar stimuli to greater amplitude to novel stimuli at occipital leads, the IDM group appears delayed in this transition in comparison with the control group). This developmental delay hypothesis is supported by the iron-deficient rodent data. For example, between postnatal day 15 (approximately a 2-month-old human) and at postnatal day 30 (approximately a $>$2-year-old human) where on certain hippocampal CA1 metrics (dendritic arborization, Jorgenson *et al*., 2003; NR2B receptor appearance, Jorgenson *et al*., 2003; and LTP, Jorgenson *et al*., 2004), the iron-deficient animals show characteristics of a younger aged animal. Although early indicators suggest that they do catch up eventually, the developmental delay hypothesis is one we have been working on in the basic model, and although it remains speculative, the data generally support the concept.

One way to determine if the "developmental delay" hypothesis is correct in this case is to continue to follow the cohort over time. We recently published findings from the larger longitudinal sample when the children were approximately 42 months of age (Riggins *et al*., 2009a, see Table IV for summary). Electrophysiological responses at occipital leads were not examined in that report, so we analyzed group differences in peak amplitude measures from that dataset (which contained 20 control

Table IV
Summary of Group Difference Findings at 12, 24, and 42 Months

| | 12-Month Assessment | 24-Month Assessment | 42-Month Assessment (Riggins *et al*., 2009a) |
|---|---|---|---|
| *Behavioral measures* | | | |
| Immediate recall | None | None | IDM < control only on difficult task |
| Delayed recall | IDM < control | None | IDM < control only on moderate task |
| Interleaved presentation | None | None | n/a |
| *Electrophysiological measures* | | | |
| Nc amplitude (midline leads) | *Control:* novel > familiar at Cz<br>*IDM:* novel > familiar at Fz | None | None |
| Nc amplitude (occipital leads) | *Control:* novel = familiar<br>*IDM:* novel < familiar | *Control:* novel > familiar<br>*IDM:* novel = familiar | None |
| Slow wave activity | Controls > IDMs | Controls > IDMs | Controls > IDMs |

and 13 IDM participants) to familiar and novel stimuli at occipital leads (O1 and O2). There were no differences between the groups in their ERP responses to familiar and novel stimuli. Thus, perhaps by early childhood, the differential responses observed over occipital leads (possibly reflecting allocation of attentional resources) have resolved and are comparable between IDMs and controls.

Unfortunately, the same conclusion cannot be made regarding memory deficits, as group differences in memory performance were still apparent at the 42-month assessment when task demands were increased (Riggins *et al*., 2009a). In short, using a modification of the elicited imitation paradigm, we examined the influence of task difficulty on memory performance. Difficulty was manipulated by altering the number of enabling relations between target actions; fewer enabling relations resulted in a more difficult memory task. When all relations were enabling (the easiest condition, as there was the most external "support" for successful memory performance), there were no group differences in behavioral recall (a finding similar to that at 24 months). However, when task difficulty increased, differences in behavior emerged in both immediate and delayed recall. Interestingly, as was the case at 12 months, these differences in behavioral performance were related to measures of iron stores (ferritin) assessed at birth (see Riggins *et al*., 2009a for elaboration).

The finding of equivalent performance for sequences with the highest number of enabling relations is similar to results from the assessment at 24 months of age and suggests that with external support, memory abilities in IDMs can be brought to levels typical for the age group. However, as at both 12 and 24 months, differences in electrophysiological responses revealed that, regardless of whether behavioral performance was different or equivalent between groups, ERP indices of neural processing underlying the memory performance differed between the groups. As in the 12- and 24-month samples, slow wave activity at Cz was greater in the control compared to the IDM group (Riggins *et al*., 2009a), and was related to behavioral performance. Thus, although imitation paradigms may provide a useful tool to examine memory performance, they may not detect subtle differences or differences in underlying processes, which may ultimately be revealed as task demands increase.

In conclusion, results from this investigation suggest that, on average, IDMs are at greater risk for memory impairment as a result of the abnormal prenatal environment in which they develop. As a group, they performed more poorly than controls on measures of behavioral recall and generated different electrophysiological response patterns to familiar and novel stimuli. Relations between these two measures support the hypothesis that the observed behavioral differences likely arise from the neural processes underlying cognitive performance and not some other noncognitive factors (e.g., temperament, willingness to imitate, etc.). However, it should be noted that considerable overlap exists between the two groups: not all IDMs performed poorly and not all controls preformed well on the behavioral and electrophysiological memory assessments. This overlap is likely the result of individual differences in the amount of risk experienced for each participant. Unfortunately, identifying damage or dysfunction in *individual* neurologically asymptomatic newborns remains challenging because the sequelae of fetal risk factors such as those that characterize the diabetic pregnancy (e.g., iron deficiency) are generally not severe enough for classic neuroimaging techniques to detect. Although the combination of behavioral and electrophysiological techniques, such as those used in the present report, may allow for some indication of early adversity, at this time outcome predictions for individual infants remain difficult. Fortunately, variations in risk do not have to be left solely to chance as preventative measures can be taken. Although differences exist between IDMs and controls in declarative memory performance, these effects appear to be titrated to the degree of metabolic regulation during the prenatal period. Thus, outcomes can be improved with proper medical care. Pregnant mothers with gestational diabetes can greatly reduce the potential risk if they are educated about their

disease and take the necessary steps to better control their blood glucose levels, blood pressure, and cholesterol levels. Screening pregnant women for diabetes and iron deficiency during the last trimester and monitoring their glycemic control may greatly reduce the risk to developing memory systems.

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## Appendix

Two-step sequences used at the 12-month assessment

1. "Make a Glowball"
   "Open the lid"
   "Pull out the drawer"
2. "Make a Gong"
   "Hang up the bell"
   "Ring it"
3. "Turn on the light"
   "Put in the car"
   "Push the stick"
4. "Find Bubbles"
   "Put in the block"
   "Push it in"
5. "Make a Happy Face"
   "Open the door"
   "Push in the block"

6. "Find the Bear"
   "Slide the bar"
   "Open the door"
7. "Make a Balloon"
   "Put in the balloon"
   "Press it"
8. "Make an Airplane"
   "Unfold it"
   "Fly it"
9. "Make a Rattle"
   "Cover it"
   "Shake it"
10. "Make a Jumper"
    "Push in the ball"
    "Pop it"
11. "Go for a Duck Walk"
    "Put down the ramp"
    "Go for a walk"

Four-step sequences used at the 24-month assessment

1. "Make a Rattle"
   "Put on the bottom"
   "Put in the ball"
   "Cover it up"
   "Shake it"
2. "Make a Drum"
   "Put it together"
   "Put on the bottom"
   "Put on the drum"
   "Spin it"
3. "Make a Gong"
   "Lift it up"
   "Put on the bar"
   "Hang up the bell"
   "Ring it"
4. "Make the Worms Dance"
   "Open it up"
   "Pull it out"
   "Put it in"
   "Turn it"

5. "Make a Glow Ball"
   "Put it together"
   "Put on the ring"
   "Put in the ball"
   "Go for a ride"
6. "Make a Jumper"
   "Put on the bottom"
   "Put on the top"
   "Push in the ball"
   "Make it jump"
7. "Go for a Car Ride"
   "Put on the top"
   "Stick it on"
   "Put it in"
   "Go for a ride"
8. "Go for a bug ride"
   "Open it up"
   "Put on the ramp"
   "Push it in"
   "Go for a ride"

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