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Memory in At-risk Populations[1]

Infants and Children Who Experience Metabolic Disturbances during the Prenatal Period

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Why Study Atypical Development?

This chapter reviews our research examining infants and children at risk for developing disorders of memory as a result of metabolic disturbances during the prenatal period. Consideration of such populations is critical for at least two reasons. First, the study of atypical development can inform the study of typical development. In this context, our goal is to shed light on the neural systems involved in typical memory development by studying infants who experience perturbations in the development of such systems. This approach is similar to knock-out approaches in genetics or in the field of neuropsychology, examining patients with select brain lesions; that is, one way to infer the neural architecture underlying a specific cognitive function (e.g., memory) is to examine the brain of individuals who have incurred alterations or damage to that area (e.g., see Vargha-Khadem et al., 1997). In addition, the study of atypical development is important in its own right, since such information may (a) identify the pathophysiology underlying a specific disorder, (b) provide new ways of diagnosing at-risk infants early in life, and (c) generate new and specific treatment approaches. These advances will lead to improved long-term outcomes. Although our work focuses on one particular population, specifically, infants born to diabetic mothers (see the following text), results from these studies not only add to what is known about this particular condition, but shed light on the course of typical development and the nature of memory. For example, responses to early injury can determine whether the developing brain is initially equipotential in terms of memory function, with any region capable of taking on this function, or whether memory structures

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are prespecified and that recovery following early damage is minimal (see de Haan & Johnson, 2003, for discussion).

Rationale for Studying "Infants Who Experience Metabolic Disturbances during the Prenatal Period"

Brain development begins approximately 18 days after conception and progresses rapidly over the course of the prenatal period (Moulson & Nelson, 2008). During this time, the brain takes on both the rudimentary form and function of the mature organ. Although brain development is not complete at birth (as it continues into young adulthood), there are several events that take place during this time that do not occur later in development (e.g., initial differentiation of tissue that results in the formation of the neural tube and ultimately the brain, referred to as *neural induction* and *neurulation*). In addition, there are several events that occur more rapidly during the prenatal period than any other period in life. For example, although new neurons are generated throughout the life span in the olfactory bulb and select regions of the hippocampus (e.g., dentate gyrus), most are formed by the end of the fourth postnatal month, and the vast majority of the 100 billion neurons that comprise the human brain are prenatal in origin (Moulson & Nelson, 2008). These neurons provide the foundation for subsequent brain development, such as synaptogenesis (i.e., circuit formation), which ultimately gives rise to mature brain function.

A hallmark of brain development is that, although genetics play a large role (particularly during prenatal development), it is continually shaped by interactions with the environment in which it develops (for discussion, see Fox, Levitt, & Nelson, 2010). Environment can be conceptualized on many levels, ranging from microsystems that directly impact the child (e.g., parents) to macrosystems that indirectly influence the child (e.g., culture, social class; see Bronfenbrenner, 1979), and include both the prenatal and postnatal environment. Nutrients supplied to the brain constitute part of the microenvironment of the nervous system. In the context of our work, during the prenatal period, these influences are all filtered through the biology of the mother and impact the developing brain via alterations in the metabolic milieu. For example, in this chapter, we highlight how fluctuations in the mother's glucose levels can impact fetal glucose levels, which in turn can influence fetal insulin and oxygen levels. In addition, brain development during the prenatal period places high metabolic demands on the fetus. These include demands for both macronutrients (protein, fat, carbohydrates), micronutrients (minerals such as sodium and potassium, trace elements such as iron, iodine, and zinc, and vitamins such as Vitamin A and folic acid), and of course, oxygen (see Fuglestad, Rao, & Georgieff, 2008).

If adequate nutrients are not readily available in the environment in which the brain is developing, the typical course of development can be altered in negative ways. Many animal studies have documented that proper nutrition is essential for optimal brain development and function (Georgieff & Rao, 2001). Deleterious effects have been shown to vary across regions of the brain, with the most pronounced effects occurring in areas with the most prolonged developmental trajectories. For example, during the famine that occurred in Holland during the Second World War, offspring were initially found to be low birthweight and small for gestational age. As these children grew up, they were observed to suffer from a variety of both biological and psychological sequelae; indeed, as long as 50 years later, attentional abilities

were found to be altered in these children (de Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). The hippocampus, which plays an essential role in memory, is one structure that illustrates several principles of brain development and is particularly vulnerable: it has high metabolic demands, making it susceptible to loss of key nutrients, such as iron and oxygen; in the primate (humans in particular), it is quite mature in the early postnatal period; and yet subregions of the hippocampus, such as the dentate gryus, continue to develop for many years after birth (see Bachevalier & Vargha-Khadem, 2001; Serres, 2001; Serres & Abraham, 2008, for review of hippocampal development in non-human and human primates).

Rationale for Studying the Infant of the Diabetic Mother to Shed Light on Memory

In this section, we elaborate on the rationale for studying the infant of the diabetic mother (IDM) to shed light on neural circuitry underlying memory. Our logic is analogous to the classic lesion approach used for over 100 years in neuropsychology, which assumes that the hippocampus is critically involved in some forms of recognition memory. We hypothesize that children who sustain damage to this region will show differences or impairments on assessments that index its function. Because IDMs are at risk for altered hippocampal development through the cascade of metabolic events described in the text that follows, they will show perturbations on memory assessments (see also Bachevalier, Chapter 6, this volume).

The prenatal environment that accompanies the diabetic pregnancy is characterized by several chronic metabolic insults that can affect fetal brain development, including hyperglycemia, iron deficiency, and hypoxemia (i.e., insufficient oxygenation of the blood). Maternal diabetes, whether diagnosed before (e.g., Type I or Type II diabetes) or during pregnancy (e.g., gestational diabetes, which results from the increased insulin requirements due to the increased production of hormones in 10% of women), is characterized by hyperglycemia (i.e., high levels of glucose in the expectant mother's blood). Maternal diabetes may result in alterations to the general fetal metabolic milieu via multiple pathways; one such pathway is excess glucose passing through the placenta and causing hyperglycemia in the fetus. This 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. These two factors (i.e., fetal hyperglycemia and reactive fetal hyperinsulinemia) independently (Milley, Papacostas, & Tabata, 1986; Stonestreet, Goldstein, Oh, & Widness, 1989) and collectively (Widness et al., 1981) increase the fetal rate of oxygen consumption beyond the placental capacity to transport oxygen and cause the fetus to become chronically hypoxemic (or oxygen deficient in the blood). This 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; see Georgieff et al., 1990; Georgieff, Schmidt, Mills, Radmer, & Widness, 1992), and occurs at the expense of the developing brain (Petry et al., 1992) (see Figure 43.1). Through this and other pathways, maternal diabetes can result in fetal hyperglycemia, iron deficiency, and hypoxemia. The severity of these metabolic risk factors is tightly linked with the severity of diabetes during pregnancy; diabetes that is unregulated during pregnancy will result in the greatest risk (see Nold & Georgieff, 2004, for a comprehensive review).

Each of these chronic metabolic abnormalities has been shown to be an independent risk factor for the developing brain (e.g., Beard, 2008; Hawdon, 1999; Lozoff & Georgieff, 2006;

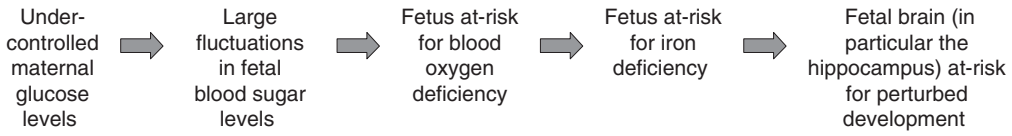

Figure 43.1 One possible pathway through which maternal diabetes can result in altered fetal brain development.

Malone, Hanna, & Saporta, 2006; Malone et al., 2008; Rao et al., 2010; Volpe, 2001; Widness et al., 1981). When these risk factors co-occur, as they do in IDMs, they combine and result in a cascade of effects that are difficult to tease apart in human studies. Due to enhanced experimental control, data from rodent models have been more successful in linking individual risk factors with specific outcomes. As mentioned in the preceding text, the hippocampus and surrounding regions exhibit rapid yet protracted development during the prenatal period; thus, this region may be especially vulnerable to disruption. 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 structures (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) (Tran, Carlson, Fretham, & Georgieff, 2008; Tran, Fretham, Carlson, & Georgieff, 2009), which is critical for 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). It is important to note that these effects occur not only during the iron-deficient period but persist into adulthood, long after complete iron repletion. Finally, the effects of prenatal iron deficiency have also been observed at the behavioral level in rodents on tasks known to be mediated by the hippocampus (e.g., swim distance on the Morris water maze and radial arm maze behavior; see Felt & Lozoff, 1996; Schmidt, Waldow, Grove, Salinas, & Georgieff, 2004, respectively).

The 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). Finally, 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).

Consistent with these findings in animal models, several studies with humans have reported adverse outcomes in children who were born to diabetic mothers. 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 measures of maternal glucose and lipid metabolism obtained late in the

diabetic pregnancy and global cognitive functioning (e.g., IQ) in middle to late childhood. These findings suggested that the severity of diabetes during pregnancy was directly related to long-term cognitive risk: the more unregulated the mother's diabetic condition, the worse the infant's cognitive outcomes. A more recent study has directly tied these impairments in global cognitive performance to fetal iron deficiency, showing specifically that newborn measures of reduced fetal iron stores were associated with diminished IQ scores at school age (Tamura et al. 2002; cf. Lucas, Morley, & Cole, 1988; Stevens, Raz, & Sander, 1999).

In studies of IDMs, iron deficiency is restricted to the prenatal period when maternal glucose levels travel across the placenta and influence fetal glucose levels. Once this influence is removed, the infant is able to regulate his/her own glucose levels (see Georgieff, Wewerka, Nelson, & de Regnier, 2002). This clarification is important since postnatal dietary iron deficiency has also been shown to produce long-term negative effects on brain development and cognitive function (e.g., Algarin, Peirano, Garrido, Pizarro, & Lozoff, 2003; Lozoff et al., 2007; Lozoff & Georgieff, 2006; Lozoff, Jimenez, & Smith, 2006). Thus, results such as those described in the preceding text (and results from our own work described in the following text) that demonstrate long-term effects of prenatal iron deficiency reflect changes that occur during the prenatal period and are not due to ongoing iron deficiency.

Studies examining the effects of diabetic pregnancy and iron deficiency on IQ in school-age children highlight their persistent nature. However, the disadvantage of using a global measure such as IQ obtained years after the proposed insult is its inability to reveal (a) specific domains of dysfunction that may be responsible for the global deficits, and (b) the specific neural circuitry that underlies deficits in behavior. Moreover, most measures of global functioning cannot easily (or meaningfully) be performed during infancy and early childhood, thereby placing limits on early detection and prediction of subsequent developmental course. In our work, we have attempted to address these limitations by (a) focusing specifically on memory function, and (b) examining the neural correlates of memory using non-invasive electrophysiological imaging (i.e., event-related potentials, or ERPs). Our study begins at birth and follows the same sample of children longitudinally through childhood (see also Nelson, 2007).

The logic of our work is as follows. First, we know that declarative memory is subserved in large part by structures that reside in the medial temporal lobe, the hippocampus in particular. Second, if the adverse fetal milieu that the IDM experiences is in fact "toxic" to the developing hippocampus, then such infants should show differences and/or impairments in memory (we use the term *impairment* when describing our findings, as we think any observed differences are deleterious). Third, because ERPs can be used to evaluate recognition memory throughout the life span (DeBoer, Scott, & Nelson, 2005; de Haan, 2007; Nelson, 1994), these measures should provide an index of alterations that do exist (although they do not allow for direct visualization of the hippocampus).

Description of the Longitudinal Cohort and Assessments Used

Our study is longitudinal in nature, although this report focuses largely on our cross-sectional findings from birth to 4 years of age (see Table 43.1). Pregnant women were recruited at approximately 28 weeks gestation from hospitals in Minneapolis/St. Paul metropolitan region.

The sample consisted of predominately Caucasian infants born to families of middle to high socioeconomic status. All women had access to standard prenatal care. Infants delivered at 32 weeks gestation or greater (as determined by maternal dates or by first trimester ultrasound)

Table 43.1 Summary of memory assessments.

Age (months)	*Electrophysiological*	*Behavioral*
0	Auditory: Mother/stranger voice	None
6	Visual: Mother/stranger face	Visual paired comparison
8	Visual: Cross-modal	Visual paired comparison
12	Visual: Elicited imitation	Elicited imitation
24	Visual: Elicited imitation	Elicited imitation
36–48	Visual: (1) Elicited Imitation, and (2) Emotion face recognition	Elicited imitation

and who had 5-minute Apgar scores equal to or greater than 6 were included. All infants (both IDM and controls) were assessed for various confounds (e.g., maternal drug use, neurological history, etc.). At time of delivery, we obtained cord blood and placental tissues so that the degree of iron deficiency could be ascertained (via ferritin, an iron-binding protein) and inferences about hypoxemia could be made (via standardized birthweight measures[2]). We began our investigation within a few days of birth and continued to follow participants through early childhood.

Event-related potentials (ERPs) were obtained at all assessments. ERPs represent the electrical activity generated by large populations of neurons that are synchronously activated which then propagates to the surface of the scalp. This activity can then be recorded by means of electrodes sitting on or near the surface of the scalp (see Figure 43.2), and appears as a series of positive and negative deflections (see Figure 43.3). Recording of ongoing activity in a continuous fashion is referred to as the electroencephalogram or EEG. When this recording is obtained during the presentation of a discrete stimulus, such as a familiar voice or face, the activity related to the processing of this stimulus can be isolated by time-locking the EEG to the presentation of the stimulus, resulting in an ERP. ERPs are typically collected from multiple trials and then averaged together in order to eliminate background noise that is not related to the stimulus of interest and, correspondingly, to increase the signal. The result is a series of positive and negative deflections, termed *components.* Each component reflects a set of functional processes with a circumscribed scalp distribution (Donchin, Ritter, & McCallum, 1978). In short, ERPs reflect changes in electrical activity of the brain in response to a discrete stimulus or event. This activity can then be compared between two conditions of interest. For example, in memory studies, responses generated by familiar stimuli can be compared to responses generated by novel stimuli. When the waveforms (or, more specifically, components within the waveforms) differ, discrimination, and thus memory, can be inferred.

ERP waveforms are composed of a series of components, some of which are peaked and others that are more distributed in time and are referred to as "slow waves." The former are thought to reflect the activation of discrete neural processes, whereas the latter are thought

[2] Exposure to hypoxemia and hyperinsulinemia was assessed via presence of neonatal macrosomia. 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, Khoury, & Mimouni, 1992; Morris, Grandis, & Litton, 1985). 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.

Figure 43.2 Example of the EEG recording cap on a 12-month-old infant. Reproduced with permission from Riggins, T., Bauer, P. J., Georgieff, M. K., & Nelson, C. A. (2010). Declarative memory performance in infants of diabetic mothers. In P. J. Bauer (Ed.), *Advances in child development and behavior, Vol. 38—Varieties of early experience: Implications for the development of declarative memory in infancy.* London, UK: Elsevier.

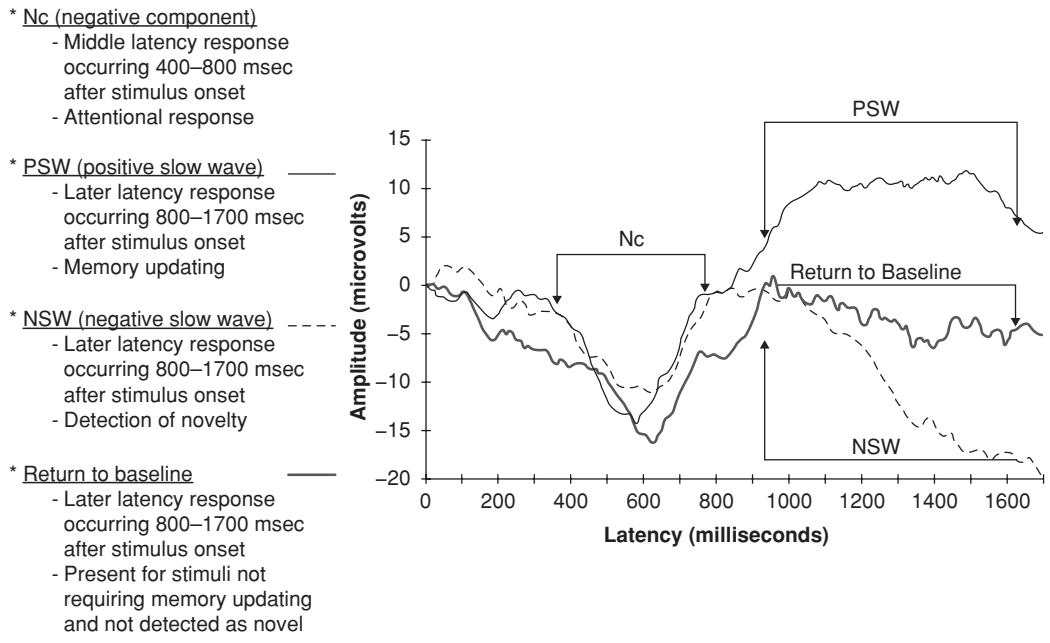

Figure 43.3 An example of different components observed in the infant event-related potential. Reproduced with permission from de Haan, M., & Nelson, C. A. (1997). Recognition of the mother's face by six-month-old infants: A neurobehavioral study. *Child Development, 68*(2), 187–210.

to reflect prolonged activity, such as cognitive processing. Examples of the former are the P2 (observed in studies of auditory recognition memory) and the Nc (or negative central component observed in studies of visual recognition memory) in infants (see Figure 43.3). In full-term infants, the P2 is a peaked positive-going component observed across midline and lateral leads that reaches its maximum approximately 200 msec post-stimulus onset. The P2 is associated with early perceptual processing of the content of the stimuli (Novak, Kurtzberg, Kreuzer, & Vaughan, 1989). The Nc is a peaked negative-going component that is maximal over fronto-central electrodes and reaches its peak approximately 500 msec after stimulus onset. The Nc reflects obligatory attention (Courchesne, Ganz, & Norcia, 1981; Nelson, 1994; Nelson, Henschel, & Collins, 1993; Richards, 2003), with larger deflections indicating greater allocation of attention (Nelson et al., 1993), and is thought to originate in regions in the frontal cortex (e.g., the anterior cingulate; Reynolds & Richards, 2005). Relevant to the work reviewed in this chapter, memory has been shown to modulate both these components (Bauer et al., 2006; Bauer, Wiebe, Carver, Waters, & Nelson, 2003; Carver, Bauer, & Nelson, 2000; Curran & Dien, 2003; de Haan & Nelson, 1997; Lukowski et al., 2005; see de Haan, 2007, for review; for a glossary of ERP components observed in the context of development, see Nelson & McCleery, 2008).

Slow waves can take the form of positive or negative distributed activity late in the waveform and, in studies of memory, are thought to reflect continued cognitive processing of the stimulus (see Figure 43.3). In most instances, these components are maximal over central and frontal scalp regions. In studies of infants, if the stimulus is one that has been fully encoded, a slow wave is not typically observed, and activity returns to baseline after earlier components. In contrast, if the stimulus has not been encoded at all, and is merely detected as novel against a background of familiar stimuli, the Nc fails to resolve, and a *negative slow wave* (NSW) is observed. Finally, if the stimulus has been only partially encoded, and requires memory updating, then the Nc returns to baseline, shifts positive, and remains positive for several hundred milliseconds (*positive slow wave* or PSW). PSW has been associated with memory or context updating (de Haan & Nelson, 1997; see also de Haan, 2007; DeBoer, Scott et al., 2005, for further discussion), is thought to originate in temporal cortices (Reynolds & Richards, 2005), and has been shown to correlate with behavioral recall in both younger infants and older children (Bauer et al., 2006; Bauer et al., 2003; Carver et al., 2000; Riggins, Miller, Bauer, Georgieff, & Nelson, 2009b).

Behavioral assessments of memory were also obtained (except at the newborn assessment). These measures served as an index of memory performance at the behavioral level and, when possible, were examined in relation to ERP measures of memory. At six and eight months, memory was evaluated via a visual paired comparison task (VPC). In this method, infants are first familiarized to an identical pair of stimuli and then tested using the familiar stimulus paired with a novel stimulus (test trials). Recognition memory is inferred when infants have a significantly longer duration of visual fixation on the novel stimulus than the familiar stimulus (Fagan, 1970; Fantz, 1964).

At the 12-, 24-, and 36–48-month assessments, a non-verbal, imitation-based method known as elicited imitation was used to index recall. In this paradigm, an adult researcher demonstrates a sequence of novel actions using props, and the participant is invited to imitate the actions modeled by the researcher either immediately (elicited imitation), after a prescribed delay (deferred imitation), or both (see Bauer, 2006, for review). Successful imitation is taken as behavioral evidence of memory for the action sequence (see Barr & Brito,

Chapter 20, this volume, Hudson & Grysman, Chapter 12, this volume, and Lukowski & Bauer, Chapter 11, this volume, for additional data from imitation-based paradigms). This technique is generally accepted as a non-verbal analogue to declarative memory report (Bauer, 2006; Bauer, DeBoer, & Lukowski, 2007; Carver & Bauer, 2001; McDonough, Mandler, McKee, & Squire, 1995), and performance on an age-appropriate analog used to test older children and adults is diminished in those with declarative memory impairments (Adlam, Vargha-Khadem, Mishkin, & de Haan, 2005; McDonough et al., 1995, respectively).

Findings to Date

Recognition of mother's voice in newborn infants

Given that the newborn infant has a very limited behavioral repertoire, we used ERPs to examine auditory recognition memory (de Regnier, Nelson, Thomas, Wewerka, & Georgieff, 2000). Specifically, based on previous work indicating that the mother's voice is familiar to the infant as a result of prenatal exposure (DeCasper & Fifer, 1980), we examined newborns' ability to discriminate their mother's voice from a stranger's voice. ERPs were recorded as infants listened (via earphones) to sound clips of their mother's voice and a stranger's voice (random 50% probabilities) pronouncing the word "baby." As a control for general auditory development, a simple auditory discrimination task was also preformed in which infants listed to speech (the sound "ba" in a female voice) vs. non-speech (computer chime) sounds. These stimuli elicited two ERP components of interest: the P2 followed by negative slow wave activity (or NSW, see the preceding text for description). In the simple auditory discrimination task, both groups showed expected ERP patterns to speech and non-speech stimuli, and there were no differences between groups, suggesting no differences in sensory processing. In the auditory recognition memory task, both the IDM and control groups demonstrated increased amplitude and latency for the P2 peak elicited by the mother's voice compared with the stranger's voice (see Figure 43.4). However, for the NSW, the control group displayed significantly greater NSW area to the stranger's voice than to the mother's, indicating discrimination, whereas no such differences were observed among IDM infants (Figure 43.4). These results suggested subtle evidence of recognition memory impairments in the IDM group despite similar sensory processing (for details, see de Regnier et al., 2000).

In a follow-up study of the preceding findings, data from the newborn period was reclassified based on the degree of iron deficiency experienced prenatally, focusing specifically on those infants we presume to be truly brain-iron deficient (ferritin <30 μg/L; see Siddappa et al., 2004). ERPs were compared between infants with brain-iron deficiency and infants who were presumably brain-iron sufficient (ferritin >30 μg/L but <60 μg/L). As in the original study, both groups showed expected ERP patterns to speech and non-speech stimuli, and no differences were apparent between groups, suggesting no differences in sensory processing. For the recognition memory task, only the brain-iron sufficient infants manifested greater NSW to the stranger's voice than to the mother's, indicating discrimination; the brain-iron deficient group showed no such difference. In fact, higher ferritin concentrations were correlated with larger negative slow waves, suggesting that the extent of iron deficiency was related to the severity of the memory impairment.

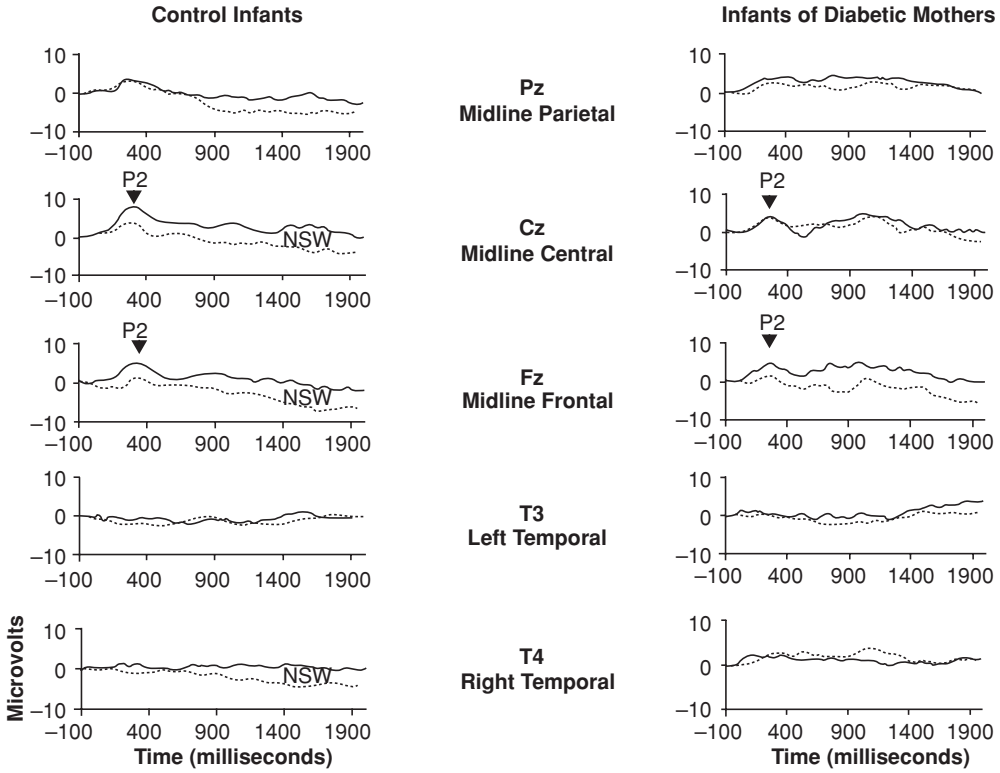

Figure 43.4 Composite (grand-average) ERPs for 28 infants in control group and 23 infants in IDM group in response to maternal (solid line) and stranger's (dotted line) voices. "P2" illustrates location of "P2" peak. Areas of significant difference between mother and stranger ERPs are denoted NSW (negative slow wave). Reproduced with permission from de Regnier, R.-A., Nelson, C. A., Thomas, K., Wewerka, S., & Georgieff, M. K. (2000). Neurophysiologic evaluation of auditory recognition memory in healthy newborn infants and infants of diabetic mothers. *Journal of Pediatrics, 137*, 777–784.

Recognition of mother's face by six-month-old infants

By six months of age, the infant's behavioral repertoire has increased substantially, as does his/her experience with world. At this age, we used a behavioral measure of memory (VPC, see preceding text) and ERPs to examine visual recognition memory (Nelson et al., 2000). Specifically, in the VPC, we examined infants' ability to discriminate a newly familiar face from a never-seen-before novel face via looking-time measures. In the ERP response, we examined infants' ability to discriminate their mother's face from a stranger's face, based on previous work indicating that six-month-old infants preferentially attend to and recognize their mother's face (de Haan & Nelson, 1997). ERPs were recorded as infants viewed visual presentations of their mother's face and a stranger's face (random 50% probabilities). These stimuli elicited the Nc (negative central component) followed by PSW (positive slow wave activity: see preceding text for description; see also Figure 43.3). Only the infants in the control group showed differential ERP responses to mother and stranger. For the Nc, controls evidenced greater activity to the mother's face versus the stranger's face; for the PSW, controls evidenced greater activity to the stranger's face versus the mother's face (Figure 43.5). This pattern was interpreted as

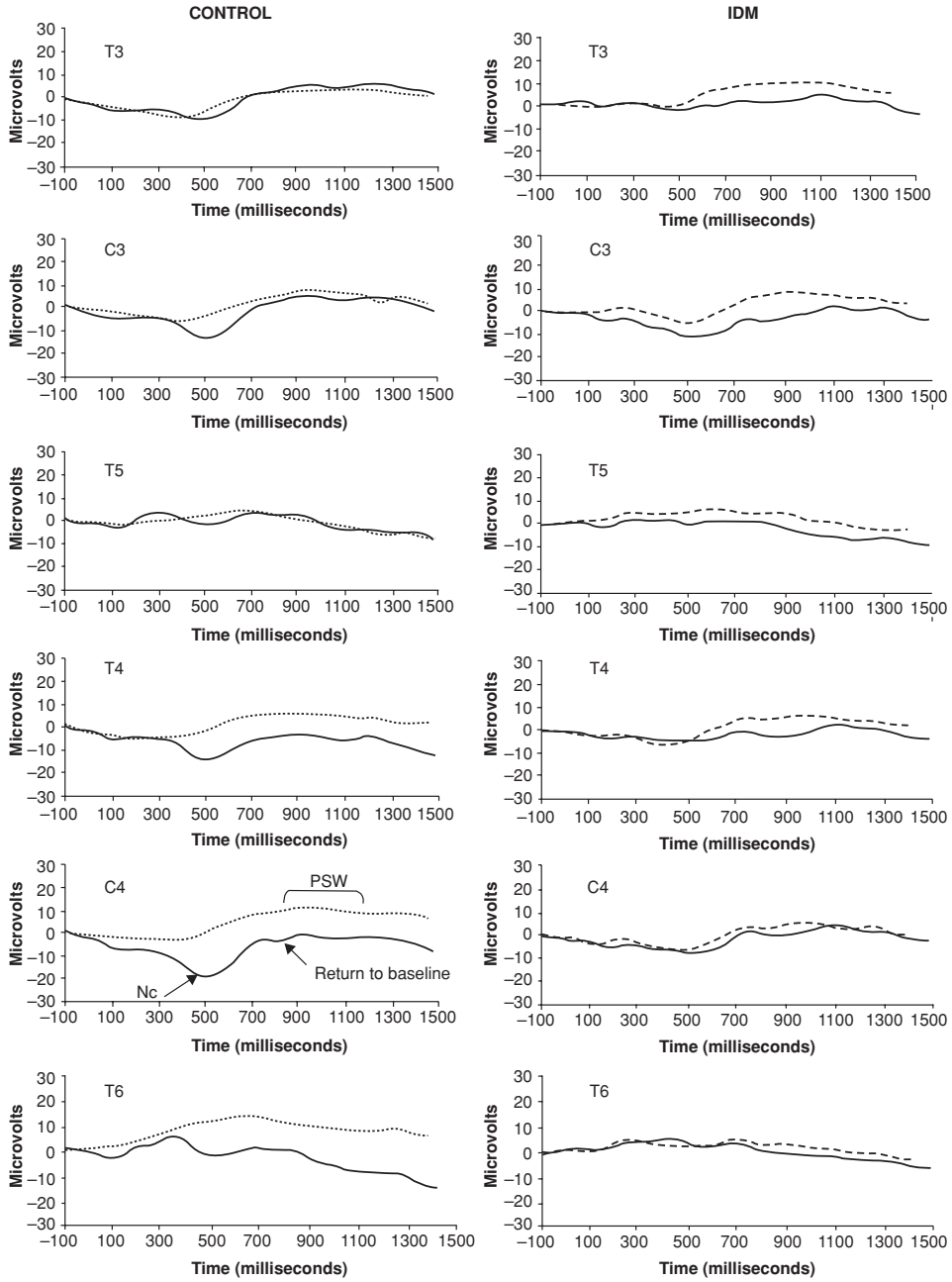

Figure 43.5 Grand mean data at lateral leads for six-month data for controls (left column) and infants of diabetic mothers (IDMs; right column). Note that the negative slow wave can most clearly be seen for lead C4 (solid line, response to mother's face) in the control data, peaking around 500 ms. Similarly, the positive slow wave (PSW) can most easily be seen in this same lead (dashed line, response to stranger's face) in the control data. Because the PSW takes the form of a distributed event-related potential response, it extends from approximately 700 ms to nearly the end of the recording epoch (1,500 ms). Nc = negative central component. Reproduced from Nelson, C. A., Wewerka, S., Thomas, K. M., Tribby-Walbridge, S., de Regnier, R.-A., & Georgieff, M. (2000). Neurocognitive sequelae of infants of diabetic mothers. *Behavioral Neuroscience, 114*, 950–956.

a reflection of their ability to encode and update their memory of the stranger's face. ERP responses in the IDM group did not differ to mother and stranger, suggesting altered attention and memory processing in this group. However, these memory differences were not detected at the behavioral level, as both groups showed novelty preferences on the VPC task. Overall, these results suggested that ERPs may be a more sensitive measure of the differences between the two groups; although there were no differences in behavioral (i.e., looking-time) measures of memory, IDMs showed patterns of electrophysiological brain activity that differed from that of controls during a memory task.

Cross-modal recognition memory in eight-month-old infants

At eight months, we evaluated cross-modal (tactile to vision) recognition memory using ERPs and a VPC task similar to the one administered at six months (Nelson, Wewerka, Borscheid, de Regnier, & Georgieff, 2003). In the cross-modal task, infants palpated an object without seeing it and were then tested on their ability to recognize that object during a visual ERP paradigm in which they viewed pictures of the object they had palpated and pictures of a novel object (random 50% probabilities). As expected, these stimuli elicited the Nc followed by PSW (see the preceding text for description). Only the infants in the control group showed differential ERP responses to the familiar and novel stimuli. For the Nc, controls evidenced greater activity to the novel object versus the familiar object[3]; for the PSW, controls evidenced greater activity to the novel object versus the familiar object (see Figure 43.6). This pattern of responses reflects their ability to encode and update their memory of the novel stimulus. Infants in the IDM group failed to show ERP evidence of distinguishing novel from familiar stimuli for either component. In the VPC task, neither group showed behavioral evidence of visual recognition memory. As at the six-month assessment, only ERP measures, not behavioral measures, differentiated between the groups.

Longitudinal development of recognition memory from birth to eight months

Using ERP data from the studies described in the preceding text (newborn, six and eight months), we examined longitudinal development of recognition memory in IDMs and controls over the first eight months of life (de Regnier, Long, Georgieff, & Nelson, 2007). IDMs were divided into high- and low-risk groups based upon iron status and weight at birth and were compared to controls. ERPs were evaluated for developmental changes in Nc and slow wave activity. Results revealed differences in developmental trajectories of the slow wave between high-risk IDMs and both low-risk IDMs and controls, who did not differ from each other. Specifically, over the left anterior temporal leads, there were no differences between groups at the newborn time period; however, over time, patterns in the high-risk IDMs diverged from patterns observed in both other groups. As illustrated in Figure 43.7, the high-risk group trend was concave-up, whereas the trend of the other two groups was concave-down. There were no differences between groups in the Nc; however, age-related patterns of development were

[3] The direction of this effect differs from that at six months of age, in which greater activity was observed to the familiar (mother) compared to the novel (stranger) stimulus. Such differences in polarity do not suggest contradictory findings, as the main index of interest for memory is simply a difference between the familiar and novel. The direction of the difference may reflect differences in allocation of processing resources driven by task difficulty or age (see Bauer et al., 2006; de Haan & Nelson, 1997, for related discussion).

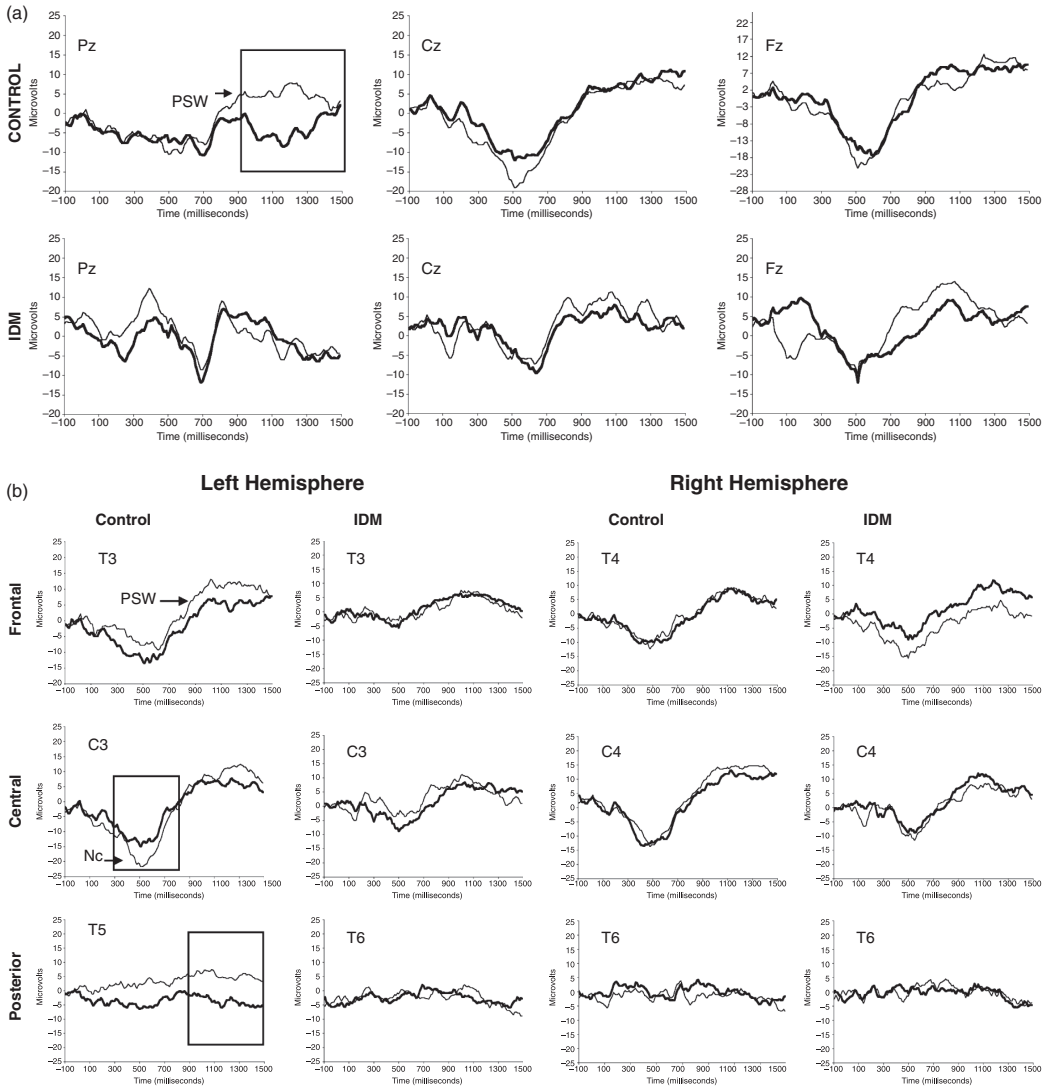

Figure 43.6 (a) Grand-average ERP data for controls (top) and IDMs (bottom), midline leads only. *Thick solid lines* represent the response to the familiar stimulus, and the *thin solid lines* represent the response to the novel stimulus. Significant PSW to novel stimulus is outlined in the control Pz panel. (b) Grand-average ERP data displaying the interaction of group (IDM, control), hemisphere (left, right), and region (posterior, central, frontal). *Thick solid lines* represent the response to the familiar stimulus, and the *thin solid lines* represent the response to the novel stimulus. Significant PSW (T3 and T5) and Nc (C3) to the novel stimulus is outlined in the control group in the left hemispheric panels. Reproduced with permission from Nelson, C. A., Wewerka, S., Borscheid, A. J., de Regnier, R.-A., & Georgieff, M. K. (2003). Electrophysiologic evidence of impaired cross-modal recognition memory in 8-month-old infants of diabetic mothers. *Journal of Pediatrics, 142*, 575–582.

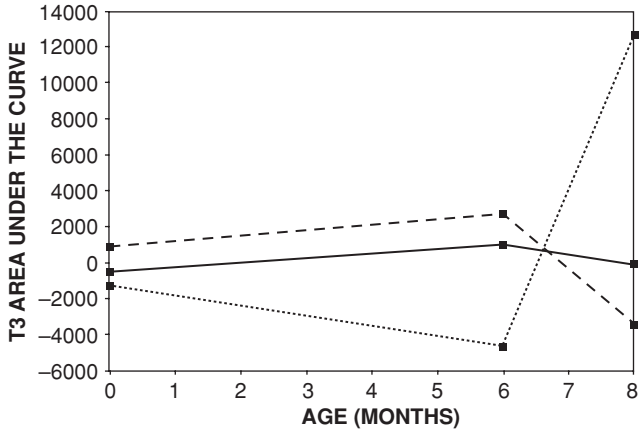

Figure 43.7 Observed T3 difference wave areas under curve (stranger–mother) by risk group and age. Solid lines indicate the mean difference wave areas for the control group. Long dashed lines indicate the mean areas for the low-risk IDMs, and the short dotted line indicates the mean areas for the high-risk IDMs. Reproduced with permission from deRegnier, R.-A., Long, J. D., Georgieff, M. K., & Nelson, C. A. (2007). Using event-related potentials to study perinatal nutrition and brain development in infants of diabetic mothers. *Developmental Neuropsychology, 31*, 379–396.

apparent such that, regardless of group, peak amplitude became more negative, and latency became shorter over time. Results of group differences in the slow wave are consistent with animal models, showing that perinatal iron deficiency affects the development of the memory networks of the brain.

General cognitive function at 12 months of age

At 12 months, we evaluated global cognitive functioning using the Bayley Scales of Infant Development (Bayley, 1993). IDMs did not differ from controls on the Mental Development or Psychomotor Development Indices (de Regnier et al., 2000; Nelson et al., 2000; cf. Nelson et al., 2003; Siddappa et al., 2004). Similar to the coarse behavioral measures at six and eight months of age (i.e., looking-time measures on the visual paired comparison task), this exam failed to discriminate between our two study populations. In addition, percentile ranks on the MacArthur Communicative Developmental Inventory (a measure of early language ability) were also similar between the groups (de Regnier et al., 2000). Thus, contrary to findings in childhood (Rizzo et al., 1991, 1997), young IDMs do not differ on global measures of cognitive function or language but, rather, only on sensitive assays of declarative memory.

Memory for event sequences in 12- and 24-month-olds

At 12 and 24 months, we evaluated memory using behavioral measures of explicit recall and electrophysiological measures of visual recognition memory (DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005; Riggins, Bauer, Georgieff, & Nelson, 2010). Behavioral measures consisted of immediate, 10-minute-deferred, and working memory (i.e., interleaved) elicited

imitation tasks. Electrophysiological measures of recognition memory consisted of a 1-week-delayed visual ERP paradigm during which infants viewed pictures of objects from one of the immediate recall elicited imitation sequences from the prior week and pictures from a novel sequence they had never seen before. At 12 months, IDMs demonstrated lower recall of event sequences after a 10-minute delay was imposed compared to the control group (DeBoer, Wewerka et al., 2005). This effect remained even after statistically controlling for individual differences in gestational age and global cognitive abilities (Mental Development Index on the Bayley Scales of Infant Development, Bayley, 1993), and was related to the amount of iron deficiency experienced prenatally (i.e., lower newborn ferritin levels were correlated with worse memory performance; see DeBoer, Wewerka et al., 2005). Differences in memory were present in measures of both Nc and PSW (negative central component and positive slow wave; see Figure 43.8a). Both groups displayed greater Nc amplitudes to novel vs. familiar stimuli, but these effects appeared over frontal leads in the IDM group and over central leads in the control group (only amplitude at the central leads was related to behavioral performance; see Riggins et al., 2010, for details). For the PSW, the control group evidenced greater slow wave activity, regardless of condition, compared to the IDM group. These results suggest that although both groups were discriminating the novel from familiar stimuli, different patterns of activation underlie this ability in the two groups. Importantly, these differences were detected despite similar performance between the groups on recall of these sequences 1-week prior.

At 24 months, there were no differences between groups in behavioral recall of event sequences. For the Nc, only the control group evidenced greater amplitudes to novel versus familiar stimuli (at occipital leads; see Figure 43.8b). This difference was not apparent in the IDM group. For the PSW, as was the case at 12 months, the control group evidenced greater slow wave activity than the IDM group regardless of condition (Figure 43.8b). Thus, although there were no differences in behavioral recall of the event sequences, there were differences in electrophysiological measures of recognition memory after a 1-week delay.

Memory for event sequences in 36–48-month-olds

Between 36 and 48 months of age, we again evaluated memory using behavioral measures of explicit recall and electrophysiological measures of visual recognition memory (Riggins, Bauer, Georgieff, & Nelson, 2009a). Behavioral measures consisted of immediate and 1-week-delayed elicited imitation tasks. In each of these conditions, memory for three different sequences of varying difficulty was examined (difficult, medium, easy). Electrophysiological measures of recognition memory consisted of a 1-week-delayed visual ERP paradigm during which subjects viewed pictures of objects from the immediate elicited imitation sequences from the prior week and pictures from a novel sequence they had never seen before. When memory demands were high, both immediate and delayed behavioral recall were significantly lower in the IDM group compared to the control group, suggesting that both encoding and retrieval processes were compromised. As at 12 months, these differences were related to the extent of prenatal iron-deficiency experienced (Riggins et al., 2009a). Results from the electrophysiological data showed that, compared to the IDM group, the control group had a shorter latency to peak of the Nc component and greater PSW activity (regardless of condition; see Figure 43.9). However, these differences were only apparent when task demands were moderate or high; when memory demands were low, there were no observable differences in performance of IDMs and controls in either behavioral or electrophysiological measures, indicating that IDMs clearly could perform the task when external support for the

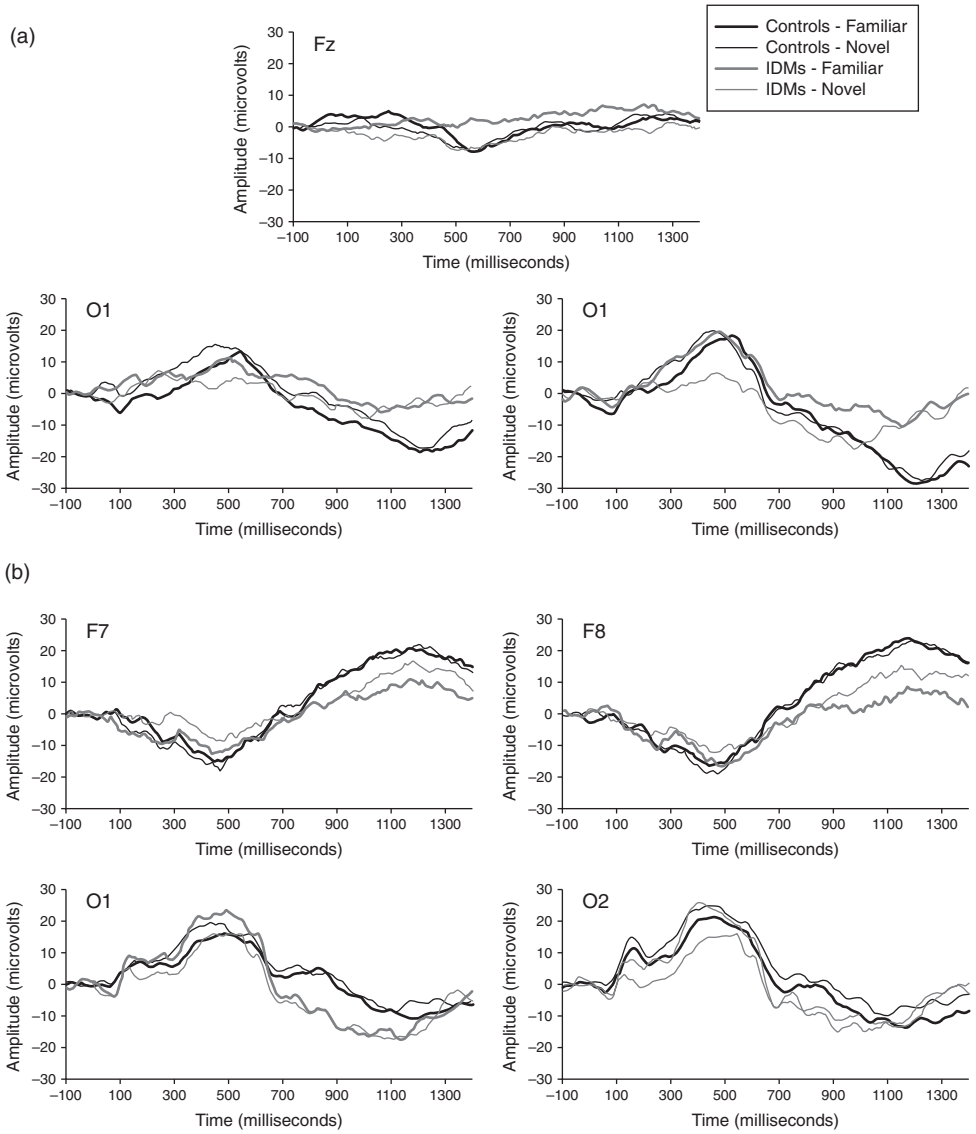

Figure 43.8 (a) Grand-averaged ERPs to familiar and novel stimuli for 12-month-old control and IDM groups. (b) Grand-averaged ERPs to familiar and novel stimuli for 24-month-old control and IDM groups. Adapted from Riggins, T., Bauer, P. J., Georgieff, M. K., & Nelson, C. A. (2010). Declarative memory performance in infants of diabetic mothers. In P. J. Bauer (Ed.), *Advances in child development and behavior, Vol. 38—Varieties of early experience: Implications for the development of declarative memory in infancy*. London, UK: Elsevier.

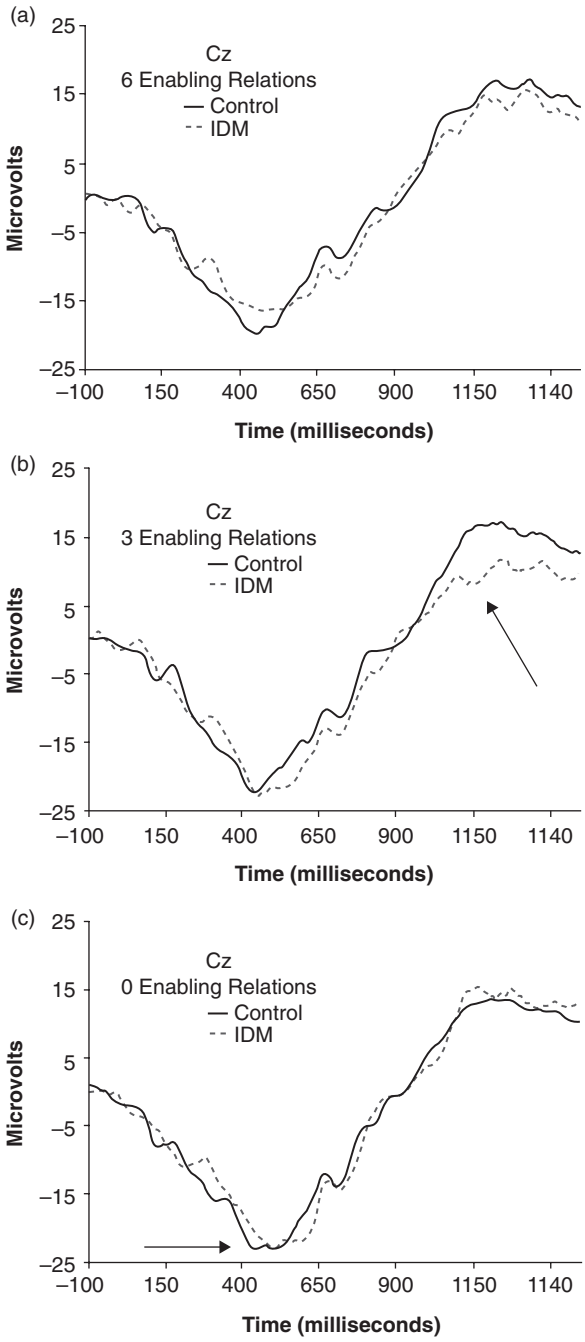

Figure 43.9 ERP waveforms recorded from the vertex for both control (solid) and IDM (dashed) groups as a function of sequence type (as determined by internal organization). Arrows indicate significant group difference. Reproduced with permission from Riggins, T., Miller, N. C., Bauer, P. J., Georgieff, M. K., & Nelson, C. A. (2009a). Consequences of maternal diabetes mellitus and neonatal iron status on children's explicit memory performance. *Developmental Neuropsychology, 34*(6), 762–779.

to-be-remembered items was greatest. Thus, at this age, for the first time, we were able to demonstrate that the dysfunction in IDMs appears to be modulated by the nature and extent of the demands placed on the circuitry (cf. de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006).

Facial expression recognition in 36–48-month-olds

Between 36 and 48 months of age, we also examined the recognition of facial expressions (Cordon, Georgieff, & Nelson, 2009). ERPs were collected as children viewed three facial expressions (happy, fear, anger). An oddball paradigm was employed, with happy facial expressions as the most frequently presented stimulus and two negative expressions (i.e., fear, anger) presented less frequently. Because happy facial expressions are probably the most common expressions that infants and young children see, and because they are one of the earliest expressions infants appear to discriminate (see reviews by de Haan & Nelson, 1998; Leppänen & Nelson, 2006; Walker-Andrews, 1997), we hypothesized that happy expressions would be highly familiar and provide a point of comparison to other expressions (notably negative expressions) that infants and young children experience less frequently. In this manner, the current task does elicit memory-related systems.

Results showed that, although both control and IDMs demonstrated differential processing to faces as a function of emotional expression, these patterns differed between IDMs and controls for both early and late ERP components (see Figure 43.10; due to space constraints, only the latter are reported, as these components have already been introduced; see Cordon et al., 2009, for details on early components). For example, for the Nc (or N400, as it is referred to in Cordon et al., 2009) controls showed a decrease in latency in the right hemisphere from 3 to 4 years of age, whereas the latency (and amplitude) increased among IDMs. For PSW, IDMs showed an increase in activity with age, whereas the controls showed a decrease. Overall, these findings suggest deviations and delayed maturational processes in attention and memory among IDMs that persist through age 4 years. Moreover, these results suggest the possibility that subtle impairments in memory can have cascading effects. The ability to discriminate and recognize a range of emotional facial expressions plays a critical role in human interactions. Disruptions in the development of face recognition, which is in part dependent on intact memory circuitry, can have negative consequences for children's emotional and social development (e.g., Parker, Nelson, & BEIP Core Group, 2005; Pollak, Cicchetti, Hornung, & Reed, 2000).

General cognitive function at 4 and 5 years of age

At 4 years, global cognitive functioning was evaluated using the Wechsler Preschool and Primary Scales of Intelligence—Revised (WPPSI-R, Wechsler, 1989). Mean performance for each group was well within the average range and above the expected mean for the test. As was the case at 12 months, the IDM and control groups did not differ on this measure of global cognitive function (Cordon et al., 2009; Sesma, Townsend, Georgeiff, & Nelson, 2004; Townsend, Georgeiff, & Nelson, 2005; cf. Riggins et al., 2009a).

At 5 years, the Cambridge Neuropsychological Testing Automated Battery (CANTAB, Sahakian & Owen, 1992), a collection of non-verbal cognitive tasks administered using a touchscreen computer, was used to measure neurocognitive function in our sample (Townsend et al., 2005). Performance of the IDM group was comparable to that of the control group on

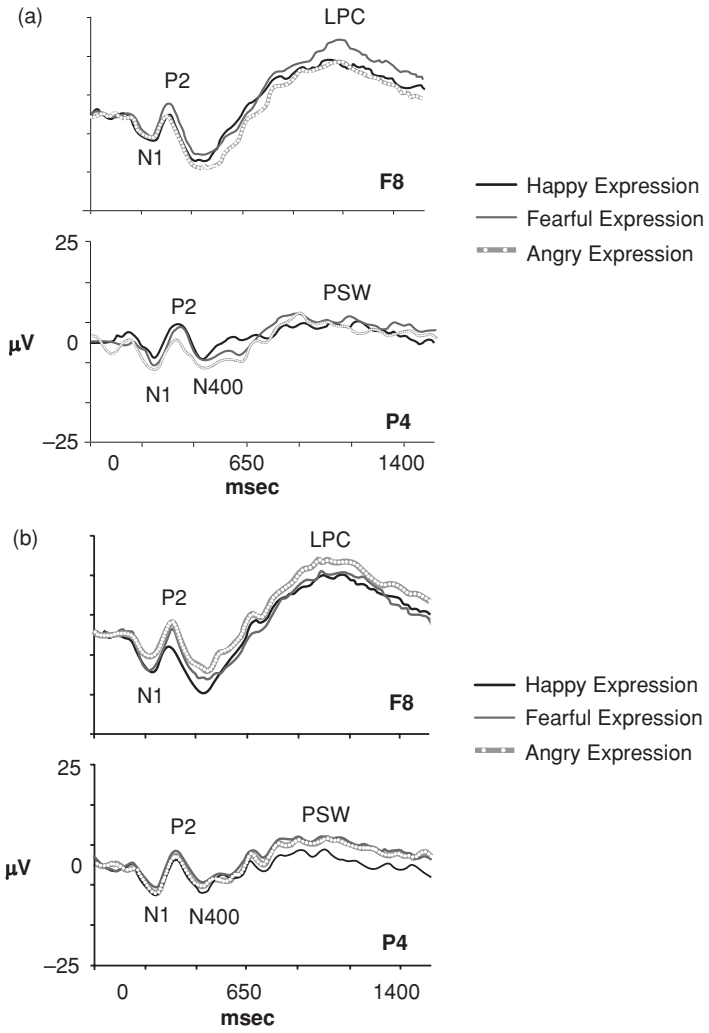

Figure 43.10 (A) Grand-average waveforms for children 36 months of age at right frontal and parietal electrodes. (B) Grand-average waveforms for children 48 months of age at right frontal and parietal electrodes. Reproduced with permission from Cordon, I. M., Georgieff, M. K., & Nelson, C. A. (2009). Neural correlates of emotion processing in typically developing children and children with diabetic mothers. *Developmental Neuropsychology, 34*(6), 1–18.

all subtests, including: psychomotor speed, fine motor accuracy, frontal lobe problem-solving, planning, and spatial memory, as well as temporal lobe recognition memory. Together with previous findings, these results suggest this behavioral assessment tool was too coarse to detect subtle dysfunction of medial temporal lobe structure/function.

Conclusions

Findings from our work reviewed in the preceding text (see Table 43.2 for summary) strongly suggest that memory is perturbed in IDMs, a population that experiences metabolic

Table 43.2 Summary of group differences for early and late ERP components at all assessments.

Assessment	*P2*	*NSW (negative slow wave)*
Newborn	Both groups: Familiar > Novel	Controls: Novel < Familiar, no difference in IDMs
	Nc (negative central component)	*PSW (positive slow wave)*
Six months	Controls: Familiar > Novel, no difference in IDMs	Controls: Novel > Familiar, no difference in IDMs
Eight months	Controls: Novel > Familiar, no differences in IDMs	Controls: Novel > Familiar, no difference in IDMs
12 months	Controls: Novel > Familiar, difference more frontal in IDMs	Controls > IDMs regardless of condition
24 months	Controls: Novel > Familiar, no difference in IDMs	Controls > IDMs regardless of condition
36–48 months	Elicited Imitation: Controls < IDMs (latency) regardless of condition Emotion Recognition: Controls < IDMS (amplitude) regardless of condition; Controls: latency decreased over time in right hemisphere; IDMs: latency and amplitude increased over time in right hemisphere	Elicited Imitation: Controls > IDMs regardless of condition Emotion Recognition: Controls > IDMs regardless of condition; Controls: amplitude decreased over time; IDMs: amplitude increased over time

disturbances during the prenatal period. This evidence was first identified a few days after birth and was consistently reported at subsequent assessments through 4 years of age.

Critically, these observed differences were shown to be related to the extent of iron deficiency experienced prenatally, which in animal models have been shown to selectively target areas that are critical for memory (e.g., hippocampus, de Ungria et al., 2000). In the newborn period, lower ferritin concentrations were correlated with less-differentiated slow wave activity between the familiar and novel stimuli (i.e., mother's vs. stranger's voice; Siddappa et al., 2004). At 12 months of age, lower newborn ferritin levels were correlated with worse memory performance on a delayed recall task (see DeBoer, Wewerka et al., 2005). At 36–48 months, lower newborn ferritin was related to lower recall on the difficult version of the task both immediately and after a 1-week delay (Riggins et al., 2009a). Across all ages, indices of other risk factors associated with the diabetic pregnancy (i.e., birthweight as a marker of chronic fetal hypoxia and hyperinsulinemia; see Nold & Georgieff, 2004) were never predictive of performance (DeBoer, Wewerka et al., 2005; Riggins et al., 2009a). It is important to note that correlations between iron deficiency and decrements in memory performance were found collapsed across groups. Although the IDM group, on average, had lower newborn ferritin levels than the control group, there was overlap in the distributions. As described earlier, severity of iron deficiency is tightly linked with the severity and control of diabetes during pregnancy. If the diabetic condition is well controlled, there is minimal risk for iron deficiency. Thus, not all participants in the IDM group experienced iron deficiency. Moreover, prenatal iron deficiency can occur for reasons other than maternal diabetes (e.g., smoking, or maternal dietary iron deficiency). Thus, regardless of group status (i.e., IDM or control), lower ferritin

levels at birth were associated with worse memory performance. In other words, an infant's iron status at birth, as indexed by ferritin, addresses the extent of metabolic irregularity experienced prenatally regardless of origin and the possible influence this will have on memory outcomes later in life. This association directly implicates effects of neonatal iron status on hippocampally based memory circuits and behavior that persist into childhood.

Differences in memory ability between groups were not always identified at the behavioral level. These results are consistent with animal models, suggesting that impairments are not absolute (Schmidt et al., 2007), but rather emerge when behavioral task demands reach a certain level of difficulty. However, at all ages, ERPs recorded during memory tasks differentiated between the groups. This suggests that ERPs may be more sensitive than behavioral measures (e.g., visual paired comparison or global intelligence assessments) when identifying integrity of the memory system. ERPs measure activity as close as possible to the neural substrates supporting this cognitive behavior; thus, these measures may be better able to detect subtle differences compared to behavioral measures that reflect cognitive activity further "downstream." Moreover, if differences are apparent in ERPs, this does not imply that differences will be present at the behavioral level, as differences in behavior also depend on additional parameters, such as the sensitivity of the behavioral index or if compensatory mechanisms are at play.

Findings from our research have several implications for current understanding of memory. First, they suggest that memory abilities may be at the core of the cognitive impairments previously reported in IDM samples at school age (Rizzo et al., 1991, 1997). We provide empirical support for the connection between the prenatal environment, development of memory circuitry, and memory performance across infancy and early childhood. The hippocampus, which is central to recognition and recall memory function, develops rapidly during late fetal life and is highly dependent on adequate nutrients (especially iron) for its development. These data speak to the atypical neural pathophysiology that impacts cognitive function in this group, and are highly valuable as they can improve diagnoses by increasing neural specificity and allowing for earlier detection. As described in the preceding text, alterations in the prenatal metabolic environment result directly from the lack of maternal glycemic control (Georgieff, 2006; Nold & Georgieff, 2004); this implies, therefore, that prevention is possible. If diabetes and maternal glucose levels are well controlled, we do not predict that the cascade of events described will occur and thus risk will be minimal. However, when prevention is not possible, findings in other cognitive domains suggest that early identification followed by intervention is likely the best course of action (Shonkoff & Phillips, 2000). Early intervention is predicated on early identification, and our work collectively demonstrates that we can distinguish individuals very early in life who might be at risk for memory impairments using proxy measures of the metabolic prenatal environment, such as neonatal or cord blood ferritin, to estimate the extent of iron deficiency and the likelihood of a long-term impact on neurobehavioral development. This may become increasingly important, as in the United States approximately 3–10% of pregnancies are complicated by abnormal glycemic control (US Food and Drug Administration, 2004; Nold & Georgieff, 2004). Of these, 80% are caused by gestational (as opposed to pre-gestational) diabetes, 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).

Results from these studies also shed light on the course of typical development. These findings suggest that memory systems are pre-specified (as opposed to equipotential; see de Haan & Johnson, 2003, for discussion), as early damage results in impairment of the function (i.e., memory) normally subserved by the damaged area (i.e., hippocampus), suggesting that

there are limits to the functional plasticity within memory (see Nelson, 2000, for discussion). Future research will need to address whether similar constraints are present regarding the extent of enhancement that is possible within memory systems.

Whether the differences identified between IDMs and controls are the result of different developmental trajectories or rather developmental delay will be addressed as we continue to follow this group. In these follow-up assessments, we will include measures to explore the presence, degree, and selectivity of hippocampal alteration using both structural and functional magnetic resonance imaging techniques (Nelson, 2007), along with sensitive neuropsychological testing and high-density ERP recordings. Our long-term goal is to assess whether the observed differences reported here fade with further development of the hippocampus and its associated memory system, or if other protective developmental factors will be revealed as we continue to track this sample over the next few years.

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