Published in final edited form as:

Dev Neuropsychol. 2009 November ; 34(6): 683–700. doi:10.1080/87565640903265129.

Neural Correlates of Emotion Processing in Typically Developing Children and Children of Diabetic Mothers

Abstract

To examine the neurocognitive sequelae of children born to diabetic mothers (CDMs), event-related potentials (ERPs) in response to three facial expressions (happy, fear, anger) were collected from 42 children (18 CDMs, 24 controls), aged 36 and/or 48 months. A linear mixed models approach was used to model individual variation in amplitude and latency. As infants, CDMs in the present study displayed subtle impairments in attention and memory processing, including face recognition, as indexed by ERPs. Findings indicate that these same children, now ages 3–4 years, continue to display ERP patterns that differ from controls in amplitude, latency, and hemispheric asymmetry.

Keywords

Memory Development; Emotion; Event-Related Potentials; Children of Diabetic Mothers

The aim of the present study was to examine the development of neural systems associated with facial expression recognition among a group of children suspected of having incurred damage to brain structures that support explicit (or declarative) memory – specifically, children born to diabetic mothers (CDMs). The fetal environment associated with the diabetic pregnancy consists of several factors (i.e., chronic hypoxia, reactive hypoglycemia, iron deficiency) that entail risk to the developing brain, particularly to areas crucial for memory (see Nold & Georgieff, 2004 for review). Previous electrophysiological findings with these same children indicated subtle deficits in attention and memory processing during infancy, including deviations in face recognition. 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). Thus, an examination of a possible association between deficits in attention and memory processing and disruptions in face processing is vital.

In the current study, we examine longitudinally the possible persistence of electrophysiological anomalies in attention and memory processing among CDMs and extend these findings to emotional stimuli (i.e., emotional facial expressions). The ability to discriminate and recognize a range of emotional facial expressions plays a critical role in human interactions, and deviations in facial expression recognition can have significant consequences for later development (e.g., Pollak et al., 2000). Because the diabetic pregnancy poses a risk to general brain development (as outlined in the next section), in addition to the specific risk posed to memory-related brain circuitry, the examination of facial expression recognition provided us with the opportunity to explore disruptions to networks that support emotion processing (albeit indirectly) in addition to those systems that support attention and memory.

Electrophysiological recording techniques, namely event-related potentials (ERPs), were employed to examine facial expression recognition. ERPs represent a measure of neural activity which in turn is believed to reflect the neural and cognitive processes involved in responding to various stimuli, events, or tasks. Additionally, because ERPs are non-invasive, ERP methodology is well-suited to study of the developing brain. ERPs, therefore, can be used

to compare the processing patterns of children who have been affected by adverse situations or are affected by a specific disorder with the patterns of typically developing children.

Children of Diabetic Mothers

Children of diabetic mothers (CDMs) are at increased risk for long-term cognitive deficits (e.g., Rizzo, Metzger, Dooley, Cho, 1997). The fetal environment during the diabetic pregnancy is characterized by hyperinsulinemia, chronic hypoxia, iron deficiency, and intermittent acute changes in glucose status and acidemia (Nold & Georgieff, 2004). These conditions constitute significant risks to the developing brain, particularly the hippocampus (Nelson & Silverstein, 1994). Moreover, animal models indicate that gestational and postnatal iron deficiency have negative consequences for myelination (Connor & Menzies, 1996), synaptic function (Jorgenson, Sun, O'Connor, & Georgieff, 2005), brain energy metabolism (deUngria, Rao, Wobken, Luciana, Nelson, & Georgieff, 2000), and brain monoamine neurotransmitter metabolism (Beard, 2003; Beard & Connor, 2003). Thus, the diabetic pregnancy may have significant consequences, not only for the development of memory circuitry, but for neural structures (e.g., amygdala) and circuits that support other processes such as emotion.

As infants, CDMs in the current study displayed subtle impairments in attention and memory processing as indexed by brain activity patterns (i.e., ERPs). deRegnier and colleagues (2000) reported that, as newborn infants, CDMs failed to show ERP evidence of discriminating their mother's voice from a stranger's voice. This effect was highly dependent on neonatal iron status, which is an index of maternal glycemic control (Siddappa et al., 2004). At 6 months of age, these same infants failed to allocate attentional resources to familiar faces and did not distinguish mother's face from stranger's face (Nelson, Wewerka, Thomas, Tribby-Walbridge, deRegnier, & Georgieff, 2000). CDMs also failed to visually recognize an object previously experienced haptically when tested at 8 months of age (Nelson, Wewerka, Borscheid, deRegnier, & Georgieff, 2003). Other researchers have also reported disturbances in attention, motor movement, and cognitive development among CDMs (Ornøy, Ratzon, Greenbaum, Wolf, & Dulitzky, 2001; Rizzo et al., 1997).

We were thus interested in determining whether the deficits in attention and memory observed in the first year of life among CDMs would persist into the preschool period, particularly with respect to faces. Because CDMs and controls in the current study are now ages 3 and 4 years, we utilized a somewhat more complex age-appropriate recognition task, namely facial expression recognition, which would engage children and allow us to examine both memory and emotion processes.

Similar to the task used at 6 months of age, an oddball paradigm was again 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 expression 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.

It is important to note that the recognition task used in the current study differs from the task employed by Nelson et al. in important ways. In the Nelson et al. study, infants were tested on their ability to discriminate between one particular familiar stimulus with which they already had a great deal of experience (i.e., mother's face) and one novel stimulus (i.e., stranger's face) they had never experienced. In the present study, all faces presented to children were novel, with the expectation that children would learn about a particular dimension of the face (i.e., happy expressions) online and generalize their knowledge and familiarity with this emotional

expression to what they saw during the experimental procedure. Nevertheless, the current task does elicit memory-related systems and may thus provide converging (or diverging) evidence of atypical memory development among CDMs.

ERP Components

Because of the dearth of ERP studies with preschool children, it was not readily evident which ERP components would be observable among children in this age range. We thus examined all evident waveforms, with a focus on those components that could be anticipated from the extant research studies with children of similar or slightly older age (e.g., Batty & Taylor, 2006; Dawson, Webb, Carver, Panagiotides, & McPartland, 2004; de Haan, Nelson, Gunnar, & Tout, 1998; Friedman, Boltri, Vaughan, & Erlenmeyer-Kimling, 1985; Holcomb, Coffey, & Neville, 1992; Johnson, 1989).

As infants, the CDMs in the present study displayed deviations in the mid-latency negative component (NC), which is thought to reflect obligatory attention during infancy (Nelson, 1994; 1997; Richards, 2003). Similar to the infant NC, the more mature N1-P2 complex is also believed to index early automatic attentional processes (Carretie, Martín-Loeches, Hinojosa, & Mercado, 2001; Stekelenburg & de Gelder, 2003). Moreover, the N1-P2 complex can be modulated by emotional stimuli such as facial expressions (Doallo, Holguín, & Cadaveira, 2006). We therefore anticipated the presence of an N1-P2 complex and sought to determine whether CDM deficits in attentional allocation, evident in infancy, would be manifest at 3 and 4 years of age.

Because the metabolic conditions present in the diabetic pregnancy pose serious risks to fetal brain areas critical for memory, we were particularly interested in examining waveforms correlated with memory processing. One index of memory processing among older children and adults is the parietal N400. The N400 is thought to reflect semantic integration and serves as an indicator of the difficulty with which new information is processed and integrated into previously stored information (e.g., Hagoort, Hald, Bastiaansen, & Petersson, 2004). The parietal N400 can be elicited by unfamiliar faces suggesting that the N400 may be indicative of a search-like process in semantic memory (Bentin & McCarthy, 1994). Moreover, the N400 has been observed among 5-year-olds in the context of emotional facial expression recognition (de Haan et al., 1998). Thus, we were interested in determining if an N400-like component would be evident among 3- and 4-year-olds and whether CDMs would demonstrate deviations in the development of the parietal N400.

Of particular interest was the examination of a P300-like component, namely the positive slow wave (PSW), typically observed in infant studies utilizing oddball paradigms (e.g., Carver, Bauer, & Nelson, 2000; de Haan & Nelson, 1997; Richards, 2003). In an oddball paradigm, an infrequently presented stimulus is displayed against a background of frequently presented stimuli. Among adults, the infrequently presented stimulus gives rise to a positive component (P300) that peaks between 300 and 900 ms and is maximal over the parietal scalp (reviewed in Coles & Rugg, 1995). The P300 (specifically P3b) is thought to be involved in context updating or in the revision of contents in working memory (Donchin 1981; Rugg, 1995). Nelson and colleagues have speculated that, among infants, the PSW reflects the updating of working memory (de Haan & Nelson, 1997; Nelson 1994); a function analogous to that of the adult P300. Thus, it is proposed that the PSW may develop over time into the more mature P300. As infants, CDMs displayed altered PSW patterns (Nelson et al., 2000), indicative of possible deficits in memory updating. If, as proposed, the PSW anticipates the more mature P300, we might expect CDMs to show aberrant P300-like patterns (i.e., PSW) at 36 and 48 months of age as evident among CDMs at 6 months of age.

Based on previous findings with CDM infants and based on the assumption that fetal hypoxia and iron deficiency affect myelination and synaptic efficacy (e.g., Carlson, Stead, Neal, Petryk, & Georgieff, 2007; Connor & Menzies, 1990; Jorgenson et al., 2005), we predict that the ERP latencies associated with attention and memory will be prolonged among CDMs relative to controls. Additionally, this same fetal pathophysiology, which may act particularly on regions in the medial temporal lobe (e.g., hippocampus; de Ungria et al., 2000) will correlate with reduced amplitudes of memory-related components among CDMs.

Method

Participants

Seventy-three children (27 CDMs, 46 Controls) enrolled from birth as part of a larger longitudinal project participated in the present study (see Nelson, 2007, for an overview of entire project). However, only those children who provided at least 10 artifact-free trials per condition and electrode location were retained for further analyses. The final sample, therefore, included 42 children (18 CDMs, 8 females; 24 Controls, 11 females). Twenty-one children (9 CDMs, 5 females; 12 Controls, 8 females) provided data at both 36 and 48 months, offering an opportunity to demonstrate longitudinally consistent effects. The remaining children provided data at either 36 or 48 months. All procedures were conducted in accordance with the American Psychological Association guidelines and approved by the IRB at the University of Minnesota.

Measures

Obstetrics risk score—An obstetrics complication scale (adapted from Prechtl, 1967) was used to assess perinatal complications not related to maternal diabetes. Points given for diabetes or insulin use were removed from the CDMs in order to demonstrate that other than the presence or absence of diabetes mellitus, the two groups were equal in obstetrical risk (see results section).

Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R)—To estimate children's cognitive functioning, the WPPSI-R was administered to children at 48 months of age (Wechsler, 1990; see results section).

Stimuli

Stimuli consisted of 100 standardized gray-scale photographs (8 × 5 inches; Ekman, 1976) of female faces portraying six different happy facial expressions, five different fearful expressions, and five different angry expressions. Each of the 16 facial expressions was portrayed by a different female model. Images were viewed from a distance of approximately 26 inches.

ERP Methodology

The electroencephalogram (EEG) was recorded using silver-silver-chloride (Ag-Ag-Cl) electrodes referenced to Cz. Recordings were obtained from scalp sites F7, F8, P3, P4, O1, O2, and Cz, following the international 10/20 system (Jasper, 1958). Impedances were accepted if they were less than 10 kΩ. The electroculogram (EOG) was recorded using Ag-Ag-Cl electrodes placed vertically above and below one eye bisecting the midline. EEG and EOG signals were recorded using a Grass Neurodata Acquisition System Model 12A5 amplifier. The amplifier gain was set to 20,000 and EOG gain was set to 5000. The bandpass was 0.1 to 30 Hz, and a 60 Hz notch filter was engaged. Recording epochs consisted of a 100-ms baseline period, a 500 ms stimulus presentation, and a 1,200 ms post-stimulus recording period. The sampling rate for EEG recording was 100 Hz.

Task

Each child sat in front of a computer monitor and was instructed to attend to each face. An experimenter sat beside the child to monitor whether the child had seen each image. One hundred trials of female faces were presented in random order. On average, children observed 94 trials (36 months, $m = 91$ trials; 48 months, $m = 96$ trials). To elicit a P300-like component (i.e., PSW), we utilized an oddball paradigm, with happy facial expressions as the most frequently presented stimulus. Specifically, happy, fearful, and angry expressions were presented (64%, 20%, and 16% of the trials, respectively) for 500 ms, with inter-trial intervals varying from 600 to 1000 ms. The task took approximately 2.5 minutes to complete.

ERP Data Reduction

ERP data were digitized online, stored on a computer hard drive, and edited for eye movement artifacts by computer algorithm (Gratton, Coles, & Donchin, 1983). All electrodes were referenced online to Cz, and then re-referenced offline to linked mastoids. Prior to averaging, trials with excessive artifact (i.e., EEG $> \pm 150$ mV in any 50-msec window) were rejected. Individual averages were then computed for each stimulus type. To equalize the signal-to-noise ratio across stimulus types, an equal number of trials was randomly selected from the available artifact-free trials in each condition. Children who did not have a minimum of 10 artifact-free trials in each condition at each electrode location were excluded from further analysis. On average, children contributed 17 artifact-free trials in each condition at each electrode location. Individual means were used to create grand means for each stimulus type. On the basis of inspection of individual averages and grand averages, seven time windows were identified: (1) N1 (frontal; 100–230 ms); (2) P2 (frontal; 160–420 ms); (3) LPC (frontal; 650–1550 ms); (4) N1 (parietal; 100–350 ms); (5) P2 (parietal; 210–430 ms); (6) N400 (parietal; 340–560 ms); (7) PSW (parietal; 675–1650 ms). Peak amplitudes relative to the 100 ms baseline and latency to peak were determined for windows 1–2 and 4–6 and average amplitude for windows 3 (LPC) and 7 (PSW). Figures 1 and 2 display the grand mean waveforms at 36 and 48 months of age, respectively.

Data Analysis

Because of the multilevel structure (trials nested within child age, child age nested within individuals) and the unbalanced nature of the dataset, a linear mixed-effects model (or multilevel) approach (with restricted maximum likelihood estimation) was used to model individual variation in amplitude and latency over a 12-month period (36 to 48 months of age). Mixed-effects models are a powerful class of models used for the analysis of correlated data (e.g., clustered data, repeated measures), which allow for the modeling of multiple sources of variation by introducing random and fixed effects into the models (Raudenbush & Bryk, 2002). Traditional analyses, such as repeated measures ANOVAs, are not designed to accommodate clustered data, which often generate correlated errors, resulting in downwardly biased standard error estimates, overly large test statistics, and inflated Type I error rates (Barcikowski, 1981; Scariano & Davenport, 1987). Because mixed-effects models incorporate a model for the error variance, the mixed-models approach produces corrected standard error estimates that reduce the risk of Type I errors, provide more efficient effects estimates, and more powerful tests (Bagiella, Sloan, & Heitjan, 2000). Finally, a major advantage of the mixed-effects model approach, particularly with respect to the current study, is that it handles unbalanced designs more efficiently, leading to more reliable conclusions. Specifically, mixed-effects models utilize data from all participants, even those not seen at every assessment, as long as data are missing at random (Rubin, 1976; for review see Dingle, Liang, & Zegler, 1994).

The initial model included the following factors: (1) age at test, coded 0 = 36 months, 1 = 48 months; (2) hemisphere location, coded 0 = left, 1 = right; (3) emotion, coded 0 = happy, 1 =

fear, and 2 = anger; and (4) group status, coded 0 = control, 1 = CDM. In addition to these variables, two- and three-way interactions were included. The initial model was estimated, evaluated, and then simplified by removing non-significant effects, with the constraint that a model could not be simplified further if it violated the hierarchy principle (i.e., lower-order factors could not be removed if a significant higher-order interaction that included the same factors was present). Each model was evaluated against the initial model using the Bayesian Information Criterion (BIC; see Verbeke & Molenberghs, 2000). Models with smaller BIC values were preferred.

Results

Preliminary analyses indicated that control children and CDMs did not differ significantly in gestational age (Controls = 38.40, $SD = 2.55$; CDMs = 37.94, $SD = 1.47$), birthweight (Controls = 3430.00 grams, $SD = 661.00$; CDMs = 3432.00 grams, $SD = 536.00$) Obstetrics Risk Score (Controls = 3.30, $SD = 1.74$; CDMs = 4.29, $SD = 1.92$), and WPPSI-R full-scale IQ score (Controls = 111.00, $SD = 15.71$; CDMs = 118.00, $SD = 15.05$), $t(41) \leq 1.02$, $ps > .05$. The subsample of children contributing data at 36 months of age ($n = 30$) did not differ significantly in sample characteristics from the subsample of children contributing data at 48 months of age ($n = 34$) or from the full sample ($n = 42$), $ts(30-41) \leq 1.11$, $ps > .05$. Furthermore, children contributing data at both 36 and 48 months of age ($n = 21$) did not differ significantly with respect to sample characteristics from either the full sample or from those children contributing data at one of the two time periods $ts(20) \leq .95$, $ps > .05$. Thus, children at all stages of analysis shared similar characteristics. Preliminary analyses also indicated that the Obstetrics Risk Score and the WPPSI-R did not contribute significantly to the regression models. Thus, these two measures were not included in the following analyses.

Based on the assumption that fetal hypoxia and iron deficiency affect myelination and synaptic efficacy, we anticipated prolonged ERP latencies among CDMs, relative to controls, and reduced amplitudes of memory-related components. In particular, based on our previous findings with these same infants at 6 months of age, we expected a reduced PSW amplitude among CDMs when compared with control children.

Frontal Components

N1

Amplitude: Fixed effects estimates for the N1 component did not reveal any significant effects, $F_s \leq (2, 358) \leq 1.82$, $ps > .05$.

Latency: Fixed effects estimates indicated a significant effect of age $F(1, 358) = 29.59$, $p < .001$. The N1 latency decreased by an estimated 30.69 ms ($SD = 5.03$) from 36 months (194.59 ms, $SD = 6.11$) to 48 months of age. No other main effects were significant, $F_s \leq (2, 358) \leq 1.66$, $ps > .05$.

The effect of age, however, was qualified by a significant age $\times$ group interaction, $F(1, 358) = 3.91$, $p \leq .05$. Whereas a decrease in latency (-30.85 ms) was evident among controls across the 12-month period, the latency among CDMs increased by an estimated 19.80 ms ($SD = 9.79$) from 36 months (186.89 ms, $SD = 9.09$) to 48 months of age, $t(358) = 2.94$, $p < .01$ (Bonferroni adjustment). This finding was further qualified by a significant three-way age $\times$ group $\times$ hemisphere interaction, $F(1, 358) = 4.89$, $p = .03$. Among CDMs, the latency at the right hemisphere increased significantly by an estimated 31.30 ms ($SD = 5.54$) from 36 months to 48 months of age, $t(358) = 2.58$, $p = .01$ (Bonferroni adjustment). The latency at left hemisphere decreased by an estimated 14.26 ms ($SD = 4.86$) but did not reach the level of significance, $t(358) = 1.20$, $p > .05$. In contrast, among controls, the latency at the left hemisphere decreased

significantly by an estimated 30.85 ms ($SD = 5.56$) across the 12-month period, $t(358) = 10.32$, $p < .001$ (Bonferroni adjustment), with a slight decrease (-6.85 ms) at the right hemisphere, $t(358) = .46$, $p > .05$.

There was also a significant age $\times$ group $\times$ emotion interaction, $F(2, 358) = 6.46$, $p < .01$. Among controls, the latency associated with happy expressions decreased significantly from age 36 to 48 months by an estimated 30.69 ms ($SD = 5.57$), $t(358) = 5.44$, $p < .001$ (Bonferroni adjustment). The latency associated with fear expressions increased by an estimated 23.61 ms ($SD = 15.08$), but did not reach the level of significance, $t(358) = 1.67$, $p > .05$, and the latency associated with angry expressions did not change significantly across the 12-month period, $t(358) = .24$, $p > .05$. In contrast, among CDMs, the latency associated with fear expressions decreased (-55.91 ms, $SD = 15.09$) significantly from age 36 to 48 months, $t(358) = 3.32$, $p < .001$ (Bonferroni adjustment). The latencies associated with happy and angry expressions did not change significantly across the 12-month period, $ts(358) \leq .81$, $ps > .05$.

P2

Amplitude: Fixed effects estimates did not reveal significant effects, $F_s \leq (2, 358) \leq 2.85$, $ps > .05$.

Latency: Fixed effects estimates indicated a significant effect of age, $F(1, 358) = 4.45$, $p < .05$, and a marginally significant effect of emotion, $F(2, 358) = 3.92$, $p = .05$. With regard to age, the P2 latency decreased by an estimated 15.38 ms ($SD = 6.44$) from age 36 to 48 months. With regard to the effect of emotion, the latency associated with fear expressions was longer by an estimated 15.66 ms ($SD = 7.22$) than the latencies associated with happy (264.20 ms, $SD = 9.15$) and angry facial expressions (264.88 ms, $SD = 9.48$), $ts(358) = 2.84$, $ps < .01$ (Bonferroni adjustment). No other main effects or interactions were significant, $F_s \leq (2, 358) \leq 2.96$, $ps > .05$.

LPC

Average amplitude: Fixed effects estimates for the LPC did not reveal any significant main effects, $F_s \leq (2, 358) \leq 3.53$, $ps > .05$. There was, however a significant age $\times$ hemisphere interaction, $F(1, 358) = 4.52$, $p < .05$. The average amplitude at the right hemisphere increased by an estimated 5.28 μV ($SD = 2.30$) from age 36 months (7.82 μV , $SD = 1.65$) to 48 months, $t(358) = 3.56$, $p < .001$, whereas the average amplitude at left hemisphere remained relatively unchanged (36 months 5.35 μV , $SD = 1.54$; 48 months = 4.85 μV , $SD = 1.51$), $ts(358) \leq .32$, $ps > .05$.

There was a significant group $\times$ hemisphere $\times$ emotion interaction, $F(2, 358) = 4.62$, $p < .05$. Among CDMs, the average amplitude associated with fear and angry expressions was smaller (negative) at the right hemisphere (fear = -2.86 μV , $SD = 1.17$; anger = -4.95 μV , $SD = 1.47$) than at the left hemisphere (fear = 4.79 μV , $SD = 1.34$; anger = 3.63 μV , $SD = 1.29$), $ts(358) \geq 2.64$, $ps < .01$ (Bonferroni adjustment), whereas no significant differences were evident among controls, $ts(358) \leq 1.11$, $ps > .05$. Moreover, among controls, the average amplitude associated with happy expressions was larger at the right hemisphere (10.82 μV , $SD = 1.49$) than at the left hemisphere (5.35 μV , $SD = 1.15$), $t(358) = 3.56$, $p < .001$, whereas no significant hemispheric differences were evident among CDMs (left = 4.43 μV , $SD = 2.17$; right = 4.76 μV , $SD = 2.01$), $t(358) = 1.02$, $p > .05$.

Parietal Components

N1

Amplitude—Fixed effects estimates for the N1 component indicated a significant effect of hemisphere, $F(1, 358) = 8.41, p < .01$. The amplitude at the right hemisphere was smaller by an estimated $3.30 \mu\text{V}$ ($SD = 1.07$) than at the left hemisphere ($-6.61 \mu\text{V}, SD = 1.19$). The effect of hemisphere, however, was qualified by a significant age $\times$ hemisphere interaction, $F(1, 358) = 6.71, p \leq .01$. The amplitude at the right hemisphere decreased by an estimated $4.20 \mu\text{V}$ ($SD = 1.90$) from age 36 months ($-6.31 \mu\text{V}, SD = 1.17$) to 48 months, $t(358) = 2.81, p = .01$ (Bonferroni adjustment), whereas the amplitude at the left hemisphere remained relatively unchanged across the 12-month period (36 months = $-6.61 \mu\text{V}, SD = 1.17$; 48 months = $-6.69 \mu\text{V}, SD = 1.07$), $t(358) = .88, p > .05$.

Latency—Fixed effects estimates did not reveal significant main effects, $F_s \leq (2, 358) \leq 2.79, ps > .05$. However, there was a significant group $\times$ hemisphere $\times$ emotion interaction, $F(2, 358) = 5.66, p \leq .05$. Among CDMs, the latency for angry expressions was longer at the right hemisphere by an estimated 49.00 ms ($SD = 20.59$) than at the left hemisphere ($210.61 \text{ ms}, SD = 17.00$) $t(358) 2.58, p < .01$ (Bonferroni adjustment). The difference between hemispheres for happy and fear expressions did not reach the level of significance, $t_s(358) \leq 1.66, ps > .05$. Among controls, the difference in latencies, between right and left hemispheres, for happy, angry, and fear facial expressions were non-significant, $t_s(358) \leq 1.38, ps > .05$.

P2

Amplitude—Fixed effects estimates for the P2 component indicated a significant effect of hemisphere, $F(1, 358) = 10.43, p = .001$. The amplitude was smaller at the right hemisphere by an estimated $3.10 \mu\text{V}$ ($SD = 1.01$) than at the left hemisphere ($9.89 \mu\text{V}, SD = 1.42$). The effect of hemisphere was qualified by a significant age $\times$ hemisphere interaction, $F(1, 358) = 5.66, p \leq .05$. The right hemisphere amplitude decreased by an estimated $5.76 \mu\text{V}$ ($SD = 2.42$) from age 36 ($6.79 \mu\text{V}, SD = 0.98$) to 48 months, $t(358) = 3.23, p = .001$ (with Bonferroni adjustment), whereas the left hemisphere amplitude remained relatively unchanged across the 12-month period (36 months = $9.89 \mu\text{V}, SD = 1.42$; 48 months = $10.87 \mu\text{V}, SD = 1.52$), $t(358) = 1.32, p > .05$.

There was also a significant age $\times$ group interaction, $F(1, 358) = 4.62, p \leq .05$. The amplitude among CDMs increased by an estimated $3.09 \mu\text{V}$ ($SD = 1.43$) from age 36 months ($6.70 \mu\text{V}, SD = 2.21$) to 48 months, $t(358) = 2.55, p = .01$ (Bonferroni adjustment), whereas the amplitude among controls remained relatively unchanged across the 12-month period (36 months = $9.89 \mu\text{V}, SD = 1.52$; 48 months = $9.97 \mu\text{V}, SD = 0.74$), $t(358) = 1.32, p > .05$.

Latency—Fixed effects estimates indicated significant effects of group, $F(1, 358) = 4.24, p < .05$, and hemisphere, $F(1, 358) = 3.93, p < .05$. Specifically, the latency among CDMs was significantly longer by an estimated 19.44 ms than among controls ($315.14 \text{ ms}, SD = .820$). With respect to hemisphere, the latency at the right hemisphere was shorter by an estimated 10.63 ms than at the left hemisphere. No other effects were significant, $F_s \leq (2, 358) \leq 2.22, ps > .05$.

N400

Amplitude—Fixed effects estimates for the N400 component indicated a significant effect of hemisphere, $F(1, 358) = 5.86, p < .05$. The amplitude at the right hemisphere was smaller by an estimated $2.88 \mu\text{V}$ than at the left hemisphere. There was also a trend for the effect of group, $F(1, 358) = 3.43, p < .07$, such that the amplitude among CDMs tended to be larger than among controls.

The effect of hemisphere was qualified by a significant age $\times$ hemisphere interaction, $F(1, 358) = 7.24, p \leq .01$. The amplitude at the right hemisphere decreased by an estimated $5.48 \mu\text{V}$ ($SD = 2.41$) from age 36 ($-6.83 \mu\text{V}$, $SD = 1.19$) to 48 months, $t(358) = 2.92, p = .01$ (Bonferroni adjustment), whereas the amplitude at the left hemisphere remained relatively unchanged across the 12-month period (36 months = $-9.70 \mu\text{V}$, $SD = 1.53$; 48 months = $-11.23 \mu\text{V}$, $SD = 1.63$), $t(358) = 1.17, p > .05$.

Latency—Fixed effects estimates indicated a significant effect of hemisphere, $F(1, 358) = 7.34, p < .01$. The latency at the right hemisphere was shorter by an estimated 16.95 ms ($SD = 6.36$) than at the left hemisphere (454.34 ms , $SD = 11.09$). The effect of hemisphere was qualified by a significant age $\times$ hemisphere interaction, $F(1, 358) = 5.02, p \leq .05$. The latency at the right hemisphere decreased by an estimated 36.30 ms ($SD = 16.32$) from age 36 (437.54 ms , $SD = 7.65$) to 48 months, $t(358) = 2.94, p < .01$, (Bonferroni adjustment), whereas the latency at the left hemisphere remained relatively unchanged across the 12-month period (36 months = 454.33 ms , $SD = 11.19$; 48 months = 455.85 ms , $SD = 11.19$) $t(358) = .14, p > .05$. There was also a significant group $\times$ hemisphere interaction, $F(1, 358) = 4.97, p \leq .05$. The latency at the right hemisphere among CDMs was longer by an estimated 28.62 ms ($SD = 12.83$) relative to the left hemisphere (426.97 ms , $SD = 15.54$), $t(358) = 2.63, p = .02$ (Bonferroni adjustment). Among controls, the latency at the right hemisphere decreased significantly by an estimated 19.05 ms relative to the left hemisphere, $t(358) = 2.81, p < .01$.

PSW

Average amplitude—Fixed effects estimates for the PSW indicated significant effects of age, $F(1, 358) = 5.81, p = .01$, and emotion, $F(2, 358) = 8.70, p < .01$. With respect to age, the average amplitude decreased by an estimated $3.08 \mu\text{V}$ ($SD = 1.25$) from age 36 to 48 months. The average amplitude was larger for angry facial expressions by an estimated $2.66 \mu\text{V}$ relative to happy facial expressions ($5.67 \mu\text{V}$, $SD = 1.49$), $t(358) = 3.02, p = .01$ (Bonferroni adjustment). The effect of fear closely approached significance, $t(358) = 2.15, p < .06$. Specifically, the average amplitude associated with fearful facial expressions tended to be larger by an estimated $2.16 \mu\text{V}$ ($SD = 1.01$) than for happy facial expressions.

The effect of group approached the level of significance, $F(1, 40) = 3.46, p = .07$. The average amplitude among CDMs tended to be smaller by an estimated $4.31 \mu\text{V}$ ($SD = 2.03$) than for control children. There was also a significant age $\times$ hemisphere interaction, $F(1, 358) = 5.52, p \leq .05$. The average amplitude at the right hemisphere increased by an estimated $3.78 \mu\text{V}$ ($SD = 1.61$) from age 36 to 48 months, $t(358) = 2.50, p = .02$ (Bonferroni adjustment), whereas the amplitude at the left hemisphere remained relatively unchanged across the 12-month period (36 months $5.66 \mu\text{V}$, $SD = 1.42$; 48 months = $5.67 \mu\text{V}$, $SD = 1.42$), $t(358) = .94, p > .05$. There was also a significant age $\times$ group interaction, $F(1, 358) = 8.26, p \leq .01$. The average amplitude among CDMs increased over the 12-month period (36 months = $0.36 \mu\text{V}$, $SD = 1.00$; 48 months = $6.64 \mu\text{V}$, $SD = 1.03$), $t(358) = 2.75, p = .01$ (Bonferroni adjustment), whereas the average amplitude among controls decreased across the 12-month period (36 months = $6.67 \mu\text{V}$, $SD = 1.10$; 48 months = 3.60 , $SD = 0.96$), $t(358) = 3.14, p < .01$.

Discussion

In the present study we investigated the development of neural systems associated with emotional facial expression recognition in typically developing children and in children of diabetic mothers (CDMs), from age 36 to 48 months. A mixed-effects model approach was used to examine attention- and memory-related ERP components across the 12-month period.

Early Latency Components

As infants, CDMs in the present study were found to display alterations in attentional allocation as indexed by a mid latency negative component (Nelson et al., 2000). The more mature attention-related ERP waveforms, specifically the N1-P2 complex, are also thought to reflect early attentional processes (e.g., Doallo et al., 2006; Stekelenburg & de Gelder, 2003). Few developmental studies, however, have been conducted on the development of the N1-P2 complex. The extant developmental studies (for visual stimuli) report a general decrease in the amplitude of the N100 and in the latency of the N100 and P200 with maturation (Johnson, 1989; Holcomb, Coffey, & Neville, 1992).

Consistent with previous research, we also observed a general decrease in the latency of the N1-P2 as well as a decrease in the amplitude of the N1-P2 waveforms (at right hemisphere) with increasing age. CDMs, however, displayed amplitude and latency patterns that differed from those of controls. Among controls, the amplitude and latency of the N1-P2 complex decreased across the 12-month period. In contrast, CDMs demonstrated a general pattern of increasing (rather than decreasing) N1-P2 latency and P2 amplitude, particularly at the right hemisphere.

Decreases in amplitude and latency are generally interpreted as reflecting greater efficiency in cortical processing as a function of brain maturation, greater knowledge, and expertise (e.g., Taylor, McCarthy, Sliba, & Degiovanni, 1999). The findings from the present study suggest that the expected maturational increase in the efficiency of the N1-P2 complex (observed among controls in the present study) was not evident among CDMs. Thus, the atypical attention-related patterns observed at 6 months were still evident among CDMs at 3- and 4-years of age, supporting our hypothesis of delayed or altered myelination among CDMs.

Although both control and CDM children demonstrated differential attention to faces as a function of emotional expression, CDMs demonstrated patterns that differed from those of controls. Whereas controls displayed decreases in N1 latency to happy facial expressions and N1 and P2 increases in latency to fear expressions (consistent with previous studies, e.g., Batty & Taylor, 2006), CDMs demonstrated a decrease in N1 latency to fear expressions and an increase in N1 latency to angry expressions at the right (but not left) hemisphere over the 12-month period.

The functional significance of these group differences in attentional allocation to the emotional quality of faces is not readily apparent. Experience with specific emotional expressions has been shown to modify children's brain activity patterns (e.g., Pollak, Cicchetti, Klorman, & Brumaghim, 1997), suggesting that the development of neural systems associated with emotional facial processing is, to some extent, experience-dependent (Leppänen & Nelson, 2006, 2009). Although it cannot be completely ruled out, it seems unlikely that CDMs would have experiences with emotional expressions that differed from controls, suggesting that other mechanisms more likely account for the observed between-group differences in emotion and attention. These atypical patterns may thus be indicative of deviations in neural circuitry that underlie, among other functions, the processing of facial expressions, similar, perhaps, to other groups of young children with developmental deficits (e.g., Dawson et al., 2004; Parker et al., 2005). Further research will be necessary to determine whether CDMs display ERP patterns similar to or different from other young children with facial expression recognition deficits.

Animal models suggest that the metabolic disturbances associated with iron deficiency (a major factor in the diabetic pregnancy) have adverse (possibly irreversible) consequences for neurobiological functioning and neural development; in part, the result of decreases in myelin formation, monoamine concentrations, and dopamine receptor density, as well as changes in neurotransmitter systems (e.g., Agarwal, 2001; Beard, Chen, Connor, & Jones, 1994; Beard,

Wiesinger, & Connor, 2003; Erikson, Jones, & Beard, 2000; Erikson, Jones, Hess, Zhang, & Beard, 2001; Ben-Shachar, Finberg, & Youdim, 1985; Yehuda, 1985). The amygdala, a structure widely considered to be involved in the appraisal of emotional significance (including facial expressions; Adolphs et al., 1999; Sato, Kubota, Okada, Murai, Yoshikawa, & Sengoku, 2002), is known to be rich in iron and iron-related proteins (Hill and Switzer 1984, Tilemans, Vijver, Verhoeven, & Deneff, 1995). The amygdala, therefore, is likely to be a structure impacted by perinatal iron deficiency at some level, with adverse consequences for the processing of the emotional value of a stimulus. Golub and colleagues (2007), for instance, found that prenatally iron-deprived juvenile Rhesus monkeys demonstrated less behavioral inhibition in new and challenging environments than did controls, suggesting the absence (or at least a reduction) in the expression of negative emotions (i.e., fear and anxiety); emotions that are normally expressed in encounters with novel objects or environments but which can be disrupted by damage to the amygdala (Izquierdo, Suda, & Murray, 2005; Mason, Capitanio, Machado, Mendoza, & Amaral, 2006). Thus, group differences in the processing of emotional signal values may reflect, in part, alterations in amygdala function and connections between the amygdala and the neocortex, in addition to deviations in the development of memory-related neural circuitry. Unfortunately, the developmental consequences of iron deficiency (particularly in the context of diabetes during pregnancy) on amygdala function have not been examined, nor can we draw direct inferences about possible deviations in amygdala function from ERP methodology. Given the paucity of research on the development of the N1-P2 complex, particularly among children in this age group, these possibilities remain tentative but certainly warrant further examination.

Later Latency Components

Face processing in adults is associated with hemispheric asymmetry, such that the right hemisphere appears to play a prominent role in the processing of facial expressions (e.g., de Haan et al., 1998; Strauss & Moscovitch, 1981). A general right hemisphere bias for later latency components was observed in the present study as children viewed three emotional facial expressions. Specifically, amplitudes were generally larger at the right than at the left hemisphere for the LPC and PSW components. Moreover, the observed right hemisphere bias became more pronounced with increasing age.

However, whereas controls displayed a right hemisphere bias in response to the three emotional facial expressions, CDMs demonstrated a decrease in right hemisphere involvement over the 12-month period. In fact, the amplitude of the LPC for angry and fearful facial expressions was negative (rather than positive) at the right hemisphere. Taylor and colleagues (2001) suggest that the greater involvement of the right hemisphere with age may be indicative of increasing expertise in configural processing versus featural processing, which is associated with the left hemisphere. If correct, CDMs may be relying more on featural processing than on configural processing. These differences in strategies may have negative consequences for how emotional facial expressions are processed (e.g., slower) and understood (i.e., less accurately).

Of particular interest were group differences in the PSW waveform. At 6 months of age, CDMs did not evince an effect of familiarity as indexed by a reduced PSW waveform to familiar, relative to unfamiliar, faces (Nelson et al., 2000). The absence of the PSW was interpreted as indicative of a subtle impairment in memory updating among CDMs. Furthermore, Nelson and colleagues have proposed that the infant PSW corresponds to the more mature P300, which is also thought to reflect contextual updating in working memory.

A P300-like component was observed at parietal electrodes, namely the PSW, which was sensitive to stimulus frequency as typically observed with the P300 waveform. That is, average amplitudes were greater for less frequently presented stimuli than for more frequently presented

stimuli. In the current study, the PSW amplitude was largest for the least frequently presented expression (anger, 16%) and smallest for the most frequently presented expression (happy, 64%). This finding lends support to the proposal that the PSW may be a developmental precursor of the P300.

Similar to brain activity patterns seen at 6-months of age, the PSW waveform at 36 months was essentially absent among CDMs, suggesting a lack of item updating in working memory. However, we did observe an increase in the PSW across the 12-month period. That is, at 48-months of age, the amplitude among CDMs more closely approached the amplitude observed among controls at 36 months of age. While it may be possible that CDMs are catching up to controls at around 4-years of age, the overall evidence does not wholly support this possibility. First, CDMs demonstrated deviations in hemispheric asymmetry for the N1-P2 complex, which became more pronounced with age. Second, deviations in hemispheric asymmetry were also evident among CDMs at frontal electrodes (LPC), with deviations becoming more (rather than less) pronounced over the 12-month period. Third, whereas controls showed a decrease in latency at the right hemisphere over the 12 months for the N400 component, the latency and amplitude of the N400 increased among CDMs. Furthermore, at 48-months of age, the PSW waveform was more similar to controls at 36 months than at 48 months of age. Overall, the findings suggest deviations and delayed maturational processes in attention and memory among CDMs persist through age 4 years. In fact, group differences in brain activity patterns generally appear to increase (rather than decrease) across the 12-month period. Whether these persistent effects represent a delay in development or a lasting, though perhaps subtle, impairment is the subject of our current follow-up investigation, as our sample turns 8–10 years of age.

Alterations in brain activity patterns were particularly pronounced for negative emotional expressions (fear, anger), similar to the deviations evident at early latency components. The processing of negative emotions may thus be compromised by alterations in the development of amygdala circuitry and/or neurotransmitter systems. Moreover, because negative facial expressions probably occur with less frequency than happy facial expressions during early development, it may be that these expressions increase the difficulty of processing the emotional quality of the faces. For instance, CDMs demonstrated an increase in the latency of an N400-like waveform. Although it is uncertain if the parietal N400 observed among children in this age group is similar in function of the N400 observed among adults, the parietal N400 is thought to be an indicator of the difficulty with which new information is processed and integrated into previously stored information (e.g., Hagoort et al., 2004). Compromised brain functioning among CDMs (particularly to the hippocampus and possibly the amygdala) may adversely affect the ease with which novel information (e.g., negative facial expressions) is perceived, and understood; with negative consequences for emotional development. Altered brain activity patterns to specific emotional expressions, for instance, have been correlated with aberrant patterns in emotion processing and social behavior among at-risk groups (e.g., Parker et al., 2005; Pollak et al., 2000). More research will be necessary to more fully examine this possibility as the functional significance of the N400 waveform observed in this very young group of children remains tentative.

Conclusions

The current study provided a unique opportunity to examine the neural underpinnings of emotional facial expression recognition, across a 12-month period, among a group of typically developing children and children of diabetic mothers. The findings suggest that the neural development of facial expression recognition among CDMs diverges from that of controls across the first four years of life. Future research will be necessary to determine if these differences in brain activity lessen with maturation and/or experience or whether differences

continue to persist despite further development in neural processing, cognitive development, and experience. Moreover, further research will be necessary to more fully delineate the functional significance of later latency components (e.g., LPC, N400, PSW), given the paucity of research with children in this age range. An important question that awaits further examination is how the alterations in neural processing, observed in the present study, correspond to behavioral indices. That is, do CDMs display altered behavioral patterns in emotional face processing (e.g., speed, accuracy)? If so, CDMs may be at risk for later emotional and social problems. It is critical, therefore, to examine the functional significance of altered developmental trajectories in brain activity among CDMs.

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Figure 1.
Grand-mean waveforms for children 36 months of age at right frontal and parietal electrodes.

Figure 2.
Grand-mean waveforms for children 48 months of age at right frontal and parietal electrodes.