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INFANT EMOTIONAL WITHDRAWAL: A PRECURSOR OF AFFECTIVE AND COGNITIVE DISTURBANCE IN FETAL ALCOHOL SPECTRUM DISORDERS

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Abstract

Objectives—To test the hypothesis that emotional withdrawal is an early indicator of affective disorder in infants heavily exposed prenatally to alcohol, which is independent of alcohol-related effects on mother-infant interaction and temperament and discriminated between children later diagnosed with fetal alcohol syndrome (FAS) and partial FAS (PFAS) and predicted cognitive and affective outcomes at 5 and 9 years.

Methods—The sample consisted of Cape Coloured (mixed ancestry) infants, whose mothers were interviewed during pregnancy regarding their alcohol consumption using a timeline follow-back approach. Infant emotional withdrawal ($n = 85$) was assessed on the Alarm Distress Baby Scale at 6.5 months. Mother-infant interaction was evaluated from video recordings during free play and infant feeding at 6.5 months ($n = 127$). Infant temperament was assessed by maternal report on the EAS Temperament Survey at 13 months ($n = 119$). Socio-demographic and psychological correlates of maternal alcohol use and infant iron deficiency were examined as potential confounders. The children were diagnosed for FAS/PFAS by expert dysmorphologists at 5 years; cognitive and affective function, at 5 and 9 years.

Results—Prenatal alcohol exposure was associated with increased infant emotional withdrawal and decreased activity, but unrelated to mother-infant interaction or any other temperament measures. Children later diagnosed with FAS and PFAS at 5 years exhibited more emotional withdrawal and less responsivity and activity as infants. Infant withdrawal, responsivity, quality of interaction, and maternal sensitivity also predicted poorer IQ and affective response at 5 and 9 years. When all four infant affective measures were examined simultaneously in a regression analysis, only infant emotional withdrawal persisted as a significant predictor of 9-year IQ.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

Conclusions—This study is the first to document a direct effect of fetal alcohol exposure on emotional withdrawal in infancy. These data link prenatal alcohol to a specific aspect of infant affective function not attributable to mother-infant interaction, infant temperament, or other socioemotional aspects of the infant's environment and identify infant emotional withdrawal as an early indicator of affective disturbance, particularly in children later diagnosed with FAS and PFAS.

Keywords

infant emotional withdrawal; prenatal alcohol exposure; infant temperament; fetal alcohol syndrome; mother-infant interaction; iron deficiency; IQ; Draw-A-Person Test

Introduction

Fetal alcohol spectrum disorders (FASD) range from fetal alcohol syndrome (FAS), which entails growth retardation, microcephaly, and craniofacial dysmorphism, to alcohol-related neurodevelopmental disorder, in which the distinctive FAS dysmorphism is lacking and neurobehavioral deficits are generally less severe. Although most attention has been focused on the cognitive deficits that characterize FASD, socioemotional development is also significantly affected in children and adolescents (e.g., Carmichael Olson et al., 1997; S. Jacobson et al., 2006; O'Connor et al., 2002; Sood et al., 2001). Some investigators have suggested that the socioemotional features of FASD seen in adolescence and adulthood are "secondary disabilities" resulting primarily from poorer executive function (attention problems, impulse control, affective organization; Streissguth et al., 1996). However, given that prenatal alcohol exposure causes diffuse neurological damage, it may impact directly on affective response in ways that may be evident already in infancy, long before executive function emerges.

The diagnostic classificatory system for infants and toddlers DC: 0-3 (Zero to Three) recognized the importance of impaired affect in infancy by including a category of depression. Although withdrawal has long been recognized as a key symptom of infant depression (Spitz, 1946), the concept of infant withdrawal remains ill-defined. Brief withdrawal is normal in the mother-infant interaction when observed at a microanalytic level (e.g., Weinberg and Tronick, 1994). Sustained infant withdrawal has been described clinically, often related to maternal non-contingent responsiveness, which is observed in maternal depression (e.g., Field, 1984). Severe withdrawal is also a key feature of non-organic failure-to-thrive (Powell and Bettes, 1992) and may be seen in clinical conditions, including central nervous system disease and visual and auditory sensory impairment (Behrman et al., 1983). In addition, emotional withdrawal occurs in severe forms of malnutrition, and its disappearance is a reliable sign of recovery (Guedeney, 1997). Depressed affect has also been found in infants with iron deficiency (Lozoff et al., 1998; Carter et al., 2010), and infant withdrawal has been recognized as an element of disorganized attachment (Lyons-Ruth et al., 1993; Main and Solomon, 1986). The Alarm Baby Distress (ADBB) Scale (Guedeney and Fermanian, 2001), a measure of infant emotional withdrawal designed to assess infants who experience organic and/or social environmental insults (Matthey et al., 2005), has not previously been used to assess effects of teratogenic exposures.

This study examines the relation between prenatal alcohol exposure and three sets of measures of infant affective function—emotional withdrawal, mother-infant interaction, and infant temperament. We hypothesize that (1) infant emotional withdrawal is an early indicator of affective disorder in infants exposed prenatally to alcohol; (2) alcohol-related emotional withdrawal is independent of effects of prenatal alcohol exposure on mother-

infant interaction and infant temperamental characteristics; (3) alcohol-related infant emotional withdrawal is seen over and above effects of maternal depression, anxiety, life stress, exposure to smoking or other drugs, or infant iron deficiency; (4) children diagnosed with FAS will have been emotionally withdrawn as infants; and (5) emotional withdrawal is predictive of affective and cognitive outcomes at 5 and 9 years independent of the effects of other aspects of infant affective function.

Methods

Sample

The sample consists of 144 infants (77 males and 67 females) for whom data were available on infant withdrawal ($n=85$), mother-infant interaction ($n=127$), or infant temperament ($n=119$). The infants are from the Cape Coloured (mixed ancestry) community in Cape Town, South Africa, and are participating in a prospective, longitudinal study on the effects of heavy prenatal alcohol exposure on development (Jacobson et al., 2008; Molteno et al., 2010). A very high incidence of FAS has been documented in this population (May et al., 2000; 2007; J. Jacobson et al., 2006), which is comprised of descendants of the Khoi and San people, the original inhabitants of the region, with an admixture of white European settlers, slaves from Malaysia, and black Africans. Due to the tradition of very heavy alcohol use in this community, there is an unusually high prevalence of heavy maternal drinking during pregnancy.

Women were recruited from an antenatal clinic that serves an economically disadvantaged Cape Coloured population. Each mother was interviewed antenatally regarding her alcohol consumption both at time of recruitment and at conception, using a timeline follow-back interview (Jacobson et al., 2002). Any woman averaging at least 1.0 oz absolute alcohol (AA)/day, the equivalent of 2 standard drinks, or reporting at least 2 binge drinking episodes (at least 5 standard drinks/occasion) during the first trimester of pregnancy was invited to participate. Women initiating antenatal care at this clinic who drank <0.5 oz AA/day and did not binge drink (52 abstainers and 8 light drinkers) were also invited to participate.

Excluded were women <18 years of age and those with diabetes, epilepsy, or cardiac problems requiring treatment, as well as religiously observant Moslem women, whose religious practices prohibit alcohol consumption. Infant exclusionary criteria were major chromosomal anomalies, neural tube defects, multiple births, and seizures. Informed consent was obtained at recruitment and at the 6.5-, 12-, and 13-month and 5- and 9-year visits; oral consent, from the child at 9 years. Approval was obtained from the Wayne State University and University of Cape Town ethics committees. All women who reported drinking during pregnancy were advised to stop or reduce their intake and were offered referrals for treatment.

Alcohol and Drug Use

Each mother was interviewed about her alcohol consumption twice during pregnancy—at recruitment ($M\pm SD=24.6\pm 6.8$ wk gestational age (GA)) and later in pregnancy (33.5 ± 6.7 GA) using timeline follow-back procedures (Jacobson et al., 2002). In the recruitment interview, the mother was asked about her drinking on a day-by-day basis during a typical 2-week period around time of conception, with recall linked to specific times of day and activities. If her drinking had changed since conception, she was also asked about her drinking during the past 2 weeks and when her drinking had changed. At the later antenatal visit, the mother was again interviewed about her drinking during the previous 2 weeks. At 1-month postpartum, the mother was asked about her drinking during a typical 2-week period during the latter part of pregnancy after the previous alcohol interview. Volume was

recorded for each type of alcohol beverage consumed each day and converted to oz of AA using multipliers proposed by Bowman et al. (1975; liquor—0.4, beer—0.04, wine—0.2).

Six summary measures were constructed: oz AA/day, AA/drinking day (quantity/occasion), and frequency of drinking at conception and averaged across pregnancy. Alcohol abuse and/or dependence were diagnosed based on DSM-IV criteria using the alcohol module of the Diagnostic Interview Schedule (DIS). Each mother was also asked how many cigarettes she smoked per day and how often she used drugs, including cocaine, marijuana, and methaqualone (“mandrax”) during pregnancy. Postpartum maternal drinking was assessed at the 12-month follow-up visit using a timeline follow-back approach to assess drinking during a typical 2-week period.

Behavioral Assessments

Infant emotional withdrawal was assessed at 6.5 months for 85 infants during the maternal interview and infant examination by an examiner blind with respect to maternal alcohol history. The infant was undressed, weighed, and measured and his/her social responsiveness was noted. The ADBB scale consists of eight items: facial expression, eye contact, general level of activity, self-stimulating gestures, vocalisations, briskness of response to stimulation, capacity to engage a relationship, and infant’s capacity to attract attention relating to social behavior. Each item is rated on a 5-point scale (0 absolutely normal to 4 obviously pathological). The items are summed to provide a total score. The ADBB has been shown to have good psychometric properties and inter-rater reliability (Guedeney and Fermanian, 2001; Lopes, 2004). A cutoff score of 5 or more, suggested to identify infants at risk for suboptimal social behavior, has been validated in two different cultures (Lopes, 2004; Puura, 2004). C.M. and the late Andrea Hay (A.H.), M.A., a child clinical psychologist, both completed training using tapes supplied by Guedeney and independently scored 26 of the assessments, with an inter-observer reliability of $r=0.92$.

Mother-infant interaction was assessed at 6.5 months for 127 infants from videotaped recordings in two situations: free play (10 min) and infant feeding (about 10 min). The mother was asked to interact with her baby as she does at home. Using a method developed for an intervention program in an indigent Cape Town peri-urban community (Molteno and Tomlinson, 1997), the play interactions were coded for maternal sensitivity, infant responsivity, and overall quality of the interaction. Each of these variables was rated for the entire 10 minutes on a scale from 0-3 (0=none, 1=a little, 2=moderate, 3=a lot). Maternal sensitivity involved the mother’s showing affection, warmth, and empathy by making eye-contact, smiling or vocalizing, or gently holding or rocking the infant. Intrusive behavior included attempting interaction while the infant cried or turned away, or if the mother shook or handled the infant roughly. Infant responsivity was scored when the infant responded to the mother’s showing affection by making eye-contact, smiling, or vocalizing. Quality of interaction was scored when there was active communication, positive vocalizations, and general synchrony in joint activities. C.M. and A.H. rated 22 interactions independently; inter-observer reliabilities were $r=0.65$ for free play and $r=0.95$ for feeding.

Temperament was assessed by maternal report at 13 months and at 5 years, using the EAS Temperament Survey (Buss and Plomin, 1984), a 20-item questionnaire, which assesses emotionality, activity, shyness, and sociability. Each of these dimensions of temperament is measured by five items (e.g., tends to be shy, cries easily, likes to be with people), each of which is rated on a 5-point scale. EAS ratings were available for 119 infants at 13 months and 116 children at 5 years. Intercorrelations of the maternal ratings at these two ages were low to moderate for three of the dimensions of temperament—emotionality, activity, and shyness (see Table 5 below).

Iron status—A blood sample was collected from a finger-stick by a trained nurse at 6.5 or 12 months. A complete blood count was obtained, including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW). Infants were determined to have iron deficiency anemia (IDA) if they had Hb of <10.9g/L and RDW of >15% plus MCV of <70.0 fL or MCH of <23.0 pg (Carter et al., 2007). A continuous measure of degree of iron deficiency was constructed by averaging *z*-scores for the four indicators of iron deficiency, which loaded together on the first component of a principal components analysis. The signs for Hb, MCV, and MCH were reversed in constructing this composite measure so that a higher score indicated a greater degree of deficiency.

Child Assessments

In September 2005, we organized a clinic at which each child was examined for growth and FAS anomalies using a standard protocol (Hoyme et al., 2005) independently by two expert FAS dysmorphologists, who subsequently reached agreement regarding FAS diagnosis. There was substantial agreement between the two U.S.-based dysmorphologists on their assessments of all dysmorphic features, including palpebral fissure length and philtrum and vermilion ratings based on the Astley and Clarren (2001) rating scales (*r* values = 0.80, 0.84, and 0.77, respectively), and between them and the Cape Town-based dysmorphologist (median *r*=0.78), who evaluated seven children who missed the clinic.

At 5 years, the children were administered the *Junior South African Individual Scales* (JSAIS; Madge et al., 1981). The JSAIS is a standardized IQ assessment, available in Afrikaans and English that has been normed for South African children. The Wechsler Intelligence Scales for Children--Fourth Edition (WISC-IV) was administered at the 9-year follow-up assessment. In addition to Full Scale IQ, the WISC-IV provides four index scores: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. IQ scores on the 5-year JSAIS were strongly correlated with the 9-year WISC-IV scores, *r*=0.67 *p*<.001. Testing was conducted in Afrikaans or English, depending on the primary language of instruction in the child's school.

In addition, we asked the child to draw a person (see Draw-A-Person Test (DAP); Harris, 1963). Following Tharinger and Stark (1990), the drawings were scored for the presence of a happy (smiling), sad (frowning/unhappy), neutral, or incomplete face (missing facial features including the mouth), or as unable to be scored. Tharinger and Stark found that children with mood disorders (not including anxiety) produced significantly fewer happy faces than controls, leading them to suggest that the absence of a happy face is likely indicative of depression. In our Detroit Longitudinal Cohort, we found that teachers reported higher Internalizing scores on the Teacher Report Form (Achenbach, 1991) for children who drew fewer happy faces, confirming that this assessment may provide a good measure of depression in young children (Corobana et al., 2003). We also found that prenatal alcohol exposure was associated with fewer happy faces in that cohort.

Control Variables

Eighteen control variables were assessed to adjust for potential confounding: (1) four sociodemographic measures collected prenatally—socioeconomic status (SES) assessed on the Hollingshead (1975) Four Factor Index and maternal age at delivery, education, and non-verbal cognitive competence assessed on the Raven Progressive Matrices (Raven et al., 1996); (2) six measures of maternal emotional function—perceived life stress on the Life Events Scale (Holmes and Rahe, 1967) collected at the 12-month visit; the mean of maternal depression data collected on the Beck Depression Inventory (BDI; Beck et al., 1996) prenatally and at 6.5- and 12-month visits, and the Edinburgh Postnatal Depression Scale

(EPDS; Cox et al., 1987) and the Structured Clinical Interview for DSM-IV (SCID) Major Depression Module, both administered at 6.5-month visit; and trait and state anxiety on the Spielberger State-Trait Anxiety Scale (1983) at prenatal visit; (3) maternal marijuana (days/week) and smoking during pregnancy (cigarettes/day) collected at prenatal visits, and postpartum alcohol use, collected at 12-month visit; and (4) infant gender, age at assessment, birth weight, GA, and iron deficiency. Because only four women reported using methaqualone during pregnancy and only one reported cocaine use, there were too few to control for these exposures in multivariate analyses; instead we reran the analyses without their infants to see if the alcohol effects continued to be evident.

Data Analysis

All variables were checked for normality of distribution. AA/day at conception and during pregnancy were positively skewed (skew >3.0) and normalized by means of log (X + 1) transformation. Pearson correlation was used to examine the intercorrelations among the measures of infant affective function—infant withdrawal, mother-infant interaction, and infant temperament—and the relation of those measures to the sociodemographic and maternal control variables. Multiple regression was used to examine the relation of prenatal alcohol exposure to the infant withdrawal, mother-infant interaction, and infant temperament measures. All control variables even weakly related to each of these outcomes (at $p < .10$) were controlled statistically in the regression analyses examining effects on those outcomes. Because the iron assessments were missing for 7 children on infant withdrawal and 32 for the mother-infant measures, separate regression analyses were conducted to control for iron deficiency together with the other potential confounders. Analysis of variance was used to examine the degree to which infant withdrawal predicted 5-year FAS diagnoses. Pearson correlations were used to examine the relation of the infant affective measures to 5- and 9-year IQ and child affective function assessed on the DAP.

Results

Sample

The mothers were poorly educated. Only 17.4% completed high school; two had no formal education (Table 1). One mother who was 17.1 years of age at delivery was inadvertently included in the sample. Virtually all (90.3%) were in the two lowest Hollingshead SES tiers. More than one-third (39.3%) met criteria for moderate to severe depression on the BDI, and 22.9% met criteria for major depression on the SCID.

Although 54.9% of the mothers drank heavily at time of conception, these women did not drink on a daily basis but concentrated their drinking on 2.3 days/week at conception and 1.5 days/week across pregnancy. Among the drinkers, more than half were alcohol abusing or dependent; 12.9% met DSM-IV criteria for alcohol abuse, 38.8%, for alcohol dependence. Most (95.8%) of the 14 women reporting marijuana used it <3 days/month. A large majority smoked cigarettes, with 9.0% smoking an average of 10 or more cigarettes/day.

Relation of Infant Withdrawal to Other Measures of Affective Function and Potential Confounders

Mean ($\pm$ SD) score on infant withdrawal was 3.4 ± 3.2 (range=0-18), with 23 infants (27.1%) scoring above the threshold of 5 or more, placing them at risk for affective problems. Table 2 shows that, as expected, greater infant withdrawal was related to poorer mother-infant interaction, particularly maternal sensitivity and infant responsivity. The strongest association was the negative relation between withdrawal and infant responsivity. With regard to temperament, activity was positively related to quality of mother-infant interaction and negatively to infant withdrawal. The negative relation with withdrawal is not surprising

given that reduced mobility is a feature of the withdrawal response. Withdrawal and mother-infant interaction were unrelated to the three other EAS measures of infant temperament—emotionality, sociability, and shyness. Nor were infant withdrawal or mother-interaction related to any of the temperament measures at 5 years.

Infant withdrawal was not related to any of the sociodemographic measures except maternal education (Table 3). Nor was withdrawal related to maternal cognitive performance, depression, anxiety, life stress, or smoking or drug use during pregnancy. By contrast, quality of mother-infant interaction and EAS temperament measures were related to numerous socioenvironmental measures, including maternal SES, education, cognitive ability, depression, anxiety, and life stress. Regarding infant characteristics, withdrawal was related to lower birthweight and GA; sociability, to higher birthweight. Shyness was greater in girls; activity, in boys. Although iron deficiency anemia was not related to any of the infant affective outcomes, the continuous measure of iron deficiency was related to increased withdrawal and poorer maternal sensitivity, infant responsivity, and quality of interaction.

Effects of Prenatal Alcohol Exposure on Infant Affective Outcomes

Fetal alcohol-exposed infants exhibited more withdrawal than controls, $M \pm SD = 4.2 \pm 3.6$, compared to 2.6 ± 2.5 , respectively, $t(83) = -2.33$, $p = .02$. One-third (33.3%) of the exposed infants scored above the cut-point for risk for affective problems on infant withdrawal, compared with 18.6% of controls.

More frequent drinking at conception and during pregnancy was related to increased infant withdrawal after control for confounders (Table 4). By contrast, the relation of frequency of maternal postpartum alcohol use to withdrawal was not significant, $\beta = .19$, $p > .10$, confirming that the alcohol effect on infant withdrawal is attributable to exposure *in utero* rather than a consequence of being raised by a drinking mother. After control for confounders, prenatal alcohol exposure was not related to any of the mother-infant interaction measures and was related only to decreased infant activity on the EAS. When the regressions were rerun omitting the five infants exposed to cocaine or methamphetamine, the effects were essentially unchanged.

Additional analyses were conducted to assess whether the effect of alcohol on withdrawal was mediated by its effects on iron deficiency. When frequency of maternal drinking during pregnancy and degree of iron deficiency were entered simultaneously in a multiple regression analysis, controlling for confounders, the effects of these exposures were independent: maternal drinking, $\beta = .30$, $p < .01$; iron deficiency, $\beta = .36$, $p < .01$, indicating that both prenatal alcohol exposure and iron deficiency were related to infant withdrawal. The same effects were seen in relation to alcohol use at time of conception.

Relation of Infant Measures to FAS Diagnosis and Childhood Cognitive and Affective Outcomes

Except in the most severe cases, it is difficult to diagnose FAS or PFAS during infancy. We, therefore, examined the degree to which infant withdrawal is already apparent in alcohol-exposed infants in an analysis of variance, comparing three groups diagnosed at 5 years—FAS/PFAS ($n = 18$), heavily exposed (HE) non-syndromal ($n = 24$), and non- or minimally exposed controls ($n = 38$). There was a main effect of diagnostic group on infant withdrawal, $F(2,77) = 3.34$, $p < .05$. In *post hoc* tests, the FAS/PFAS group scored higher than both the HE group ($p = .06$) and controls, $p < .01$, suggesting that affective withdrawal can already be seen in infancy in the more severely affected children. There were no differences on infant withdrawal between the HE and control groups, $p > .20$.

Among the mother-infant interaction ratings, only infant responsivity was related to FASD diagnosis, $F(2,117)=7.41$, $p<.001$, with the FAS/PFAS group ($n=30$) showing less responsivity than the HE ($n=41$) and controls ($n=49$), $ps<.002$ and $.001$, respectively. There were main effects of FASD diagnostic group on 13-month EAS infant activity and sociability, $F(2,113)=3.78$ and $F(2,113)=8.49$, $ps<.05$ and $.001$, respectively, and an association that fell short of significance for emotionality, $F(2,113)=2.36$, $p<.10$. Infants with FAS/PFAS ($n=32$) were more irritable ($p<.05$) and less active ($p<.05$) and sociable ($p<.01$) than controls ($n=39$). No differences were found for HE ($n=43$) vs. controls, all $ps>.15$. The combination of infant outcomes that best predicted an FAS/PFAS diagnosis was examined in a multiple regression analysis with FAS/PFAS vs. control group as the outcome measure. Infant withdrawal, responsivity, and sociability jointly explained 23.6% of the variance in this diagnosis, $F(3,37)=3.80$, $p=.018$.

Infant withdrawal predicted fewer happy faces on the DAP (Table 5). The only other predictor of happy faces was greater maternal sensitivity during free play. When infant withdrawal and maternal sensitivity were entered simultaneously in a regression predicting happy faces, only the withdrawal effect was significant, $\beta=-.26$, $p<.05$; the sensitivity effect was not, $\beta=.04$, $p>.20$. None of the 10 children diagnosed with FAS drew a happy face, confirming a similar finding of an association between prenatal alcohol use and fewer happy faces in our Detroit Longitudinal Cohort at 7.5 years (Corobana et al., 2003).

Infant emotional withdrawal also predicted poorer IQ on the WISC-IV at 5 and 9 years; infant responsivity, quality of interaction, and maternal sensitivity were related to higher IQ at both ages; and more infant activity predicted higher 9-year IQ. When all four infant affective measures were included together in a multiple regression analysis, only the relation with infant emotional withdrawal was significant, $\beta=-.34$, $t=-2.05$, $p<.05$; none of the other β s were significant, all $ps>.20$.

Discussion

This study is the first to identify infant withdrawal as an affective endpoint seen early in development that is sensitive to prenatal alcohol exposure, even after control for demographic measures and maternal emotional function, smoking, and postpartum drinking. Although poorer maternal sensitivity during mother-infant interaction was also associated with increased infant withdrawal, fetal alcohol exposure contributed independently to infant withdrawal over and above the contribution of maternal sensitivity. Our findings are consistent with previous studies showing a relation between maternal non-contingent responsiveness and more sustained infant withdrawal (Cohn and Tronick, 1983; Field, 1984). The finding that infant emotional withdrawal was even more strongly related to infant responsivity than to maternal sensitivity suggests that fetal alcohol-related withdrawal may also contribute to reduced sensitivity by the caregiver.

By contrast to mother-infant interaction and the temperament measures, infant withdrawal was largely unrelated to socioenvironmental factors, including maternal depression, anxiety, and life stress. In most populations, maternal depression is associated with poorer cognitive and socioemotional development in children (e.g., Murray and Cooper, 1997). The absence of a link between maternal depression and infant withdrawal in the current study is consistent with reports from two recent studies of socially disadvantaged Australian infants (Bookless, 2004; Matthey et al., 2005), in which maternal postpartum depression was also prevalent. The absence of this association may be attributable to the social interaction provided to infants by extended family members, especially in poor families living together. Alternatively, the absence of this association in this sample suggests that infant withdrawal

may reflect a neurological impairment that is independent of the postpartum social environment and, in this case, attributable to fetal alcohol exposure.

Infant emotional withdrawal was negatively related to interactions during both free play and feeding, confirming the expected relation between mother-infant interaction and infant withdrawal. Nevertheless, none of the mother-infant relationship measures were predicted by prenatal alcohol exposure. The principal aspect of temperament associated with prenatal alcohol exposure was decreased activity level. Lower activity in the more heavily exposed infants reported by the mothers at 13 months are consistent with the blunted affective response seen in alcohol-exposed newborns (e.g., Oberlander et al., 2010; Streissguth et al., 1983). Moreover, the potential utility of infant activity as an early indicator of later temperament was demonstrated by its moderate association with EAS activity at 5 years.

The finding that infant emotional withdrawal is sensitive to iron deficiency provides further evidence of the validity of this measure since iron deficiency has been shown to be related to depressed infant affect (Lozoff et al., 1998; Carter et al., 2010). Consistent with our findings of increased infant withdrawal, iron deficient infants in Chile were less likely to show positive affect, interact socially, or to check caregiver reactions (Lozoff et al., 2003). Similarly, in a Detroit inner-city study conducted in our laboratory, iron deficient infants exhibited lower levels of positive affect and social engagement (Lozoff et al., 2008), poorer attention to photos of their mothers and other women (Burden et al., 2007), and poorer orientation and engagement when administered a cognitive task (Carter et al., 2010). As noted above, we found that prenatal alcohol exposure and iron deficiency were each independently associated with higher levels of infant withdrawal.

It is noteworthy that infant affective measures discriminated between infants subsequently diagnosed with FAS or PFAS, indicating that the affective components of these disorders are already manifest early in development. Moreover, although withdrawal, responsivity, quality of interaction, and maternal sensitivity were each predictive of higher 9-year IQ, emotional withdrawal was the strongest predictor, underscoring the importance of this feature of FASD.

In conclusion, this is the first study to link fetal alcohol exposure directly to an affective endpoint that emerges early in development, well before higher cognitive or executive function. This finding suggests that affective problems that have been described in later childhood, adolescence, and adulthood in FASD are not secondary to deficits in attention or higher order cognition. DAP, an innovative measure of childhood depression or mood disorder (Tharinger and Stark, 1990) was also predicted by the infant withdrawal measure, further supporting the hypothesis that infant withdrawal provides an early indicator of fetal alcohol-related affective disturbance. It is noteworthy that not a single child diagnosed with FAS drew a happy face at the 5-year assessment. Our analysis of the fetal alcohol diagnostic data suggests that infant affective withdrawal is particularly prevalent among the most severely affected children and predictive of later affective and cognitive outcomes. Moreover, the link between prenatal alcohol exposure and infant withdrawal was not attributable to postpartum maternal drinking, quality of mother-infant interaction, or maternal life stress, anxiety, or depression. Given the apparently direct link between exposure to alcohol *in utero* and infant withdrawal, these data suggest that affective withdrawal may constitute an early manifestation of an important aspect of the extensive socioemotional problems that characterize fetal alcohol-related disorders.

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Table 1Sample characteristics ($N = 144$)

	<i>M</i> or %	<i>SD</i>	<i>Range</i>
Maternal characteristics			
Socioeconomic status ^a	20.1	8.5	8 - 46
Age at delivery	26.8	6.2	17.1 - 43.8
Parity	2.2	1.3	1 - 8
Years of school completed	8.6	2.6	0 - 12
Percent married	31.3	---	---
Raven score ^b	28.2	10.5	6 - 55
Depression			
BDI ^c	15.3	11.6	0 - 53
SCID ^d ($n = 134$)	22.9	---	---
EPDS ^e ($n = 133$)	15.7	3.4	7 - 22
Spielberger anxiety ^f			
State	34.6	9.1	20 - 75
Trait	44.1	8.9	25 - 67
Perceived life stress ^g ($n = 117$)	17.8	18.2	0 - 102
Daily average (oz AA) ^h			
At conception ($n = 79$)	1.5	1.6	0.02 - 11.6
During pregnancy ($n = 85$)	0.9	1.0	0.01 - 7.4
Average drinks/occasion (oz AA) ^h			
At conception ($n = 79$)	4.3	2.7	0.3 - 15.4
During pregnancy ($n = 85$)	3.9	2.5	0.6 - 15.4
Number of drinking days/week ^h			
At conception ($n = 79$)	2.3	1.5	0.1 - 7.0
During pregnancy ($n = 85$)	1.5	1.1	0.03 - 6.7
Marijuana use (days/week, $n = 14$) ^h	2.4	2.0	0.03 - 7.0
Cigarettes/day ($n = 101$) ^h	7.9	6.1	0.4 - 40.0
Infant characteristics			
Gender (% male)	53.5	---	---
Gestational age (wk)	38.7	2.4	29 - 43
Birthweight (g)	2878	576	1130 - 4240
Head circumference (cm) ($n = 143$)	32.8	1.9	23 - 36

^aHollingshead Four-Factor Index of Social Status (Hollingshead, 1975) assessed prenatally. Maternal demographic data also collected at prenatal visit.

^bRaven Progressive Matrices (Raven et al., 1996) administered at prenatal visit.

^c Beck Depression Inventory (Beck et al., 1996) data collected at prenatal and 6.5- and 12-month visits from the mother were averaged for the three assessments.

^d Structured Clinical Interview for DSM-IV (SCID) Major Depression Module administered at 6.5 months.

^e Edinburgh Postnatal Depression Scale (Cox et al., 1987) administered at 6.5 months.

^f State-Trait Anxiety Inventory (Spielberger et al., 1983) administered at prenatal visit.

^g Adapted from Holmes and Rahe (1967) administered at 12-month visit.

^h Consumers only; AA=absolute alcohol.

Table 2

Associations among infant withdrawal, mother-infant interaction, and infant temperament

	Mother-infant interaction				Infant EAS temperament			
	Infant withdrawal	Maternal sensitivity	Infant responsivity	Quality of interaction	During feeding	Emotionality	Activity	Sociability
Infant withdrawal	--							
Mother-infant interaction								
During free play								
Maternal sensitivity	-.47*** (84)	--						
Infant responsivity	-.56*** (84)	.66*** (127)	--					
Quality of interaction	-.34** (84)	.71*** (127)	.71*** (127)	--				
During feeding								
Maternal sensitivity	-.36*** (83)	.40*** (125)	.34*** (125)	.44*** (125)	--			
Infant EAS temperament								
Emotionality	.08 (63)	-.07 (103)	-.04 (103)	.01 (103)	-.04 (102)	--		
Activity	-.29* (63)	.29** (103)	.21* (103)	.12 (103)	.15 (102)	-.09 (119)	--	
Sociability	-.12 (63)	.12 (103)	.15 (103)	.01 (103)	.02 (102)	-.22* (119)	.29** (119)	--
Shyness	-.07 (63)	.06 (103)	-.01 (103)	.03 (103)	-.04 (102)	.47*** (119)	-.16 [†] (119)	-.46*** (119)

Values are Pearson *rs*.

[†] *p*<.10

* *p*<.05

** *p*<.01

*** *p*<.001

Table 3

Relation of infant withdrawal, mother-infant interaction, and infant temperament with sociodemographic and other maternal and infant characteristics

	Mother-infant interaction											
	Infant withdrawal				During free play				During feeding			
	Maternal sensitivity		Infant responsivity		Quality of interaction		Maternal sensitivity		Emotionality		Infant EAS temperament	
	N	r	N	r	N	r	N	r	N	r	N	r
Maternal characteristics												
Socioeconomic status ^a	85	-.12	127	.25**		.30***	127	.14	119	-.17 [†]	.21*	.07
Age at delivery	85	.02	127	-.05		-.02	127	.05	119	.05	-.12	-.09
Parity	85	.04	127	.01		-.05	127	.04	119	.09	-.02	-.06
Education (yr)	85	-.20 [†]	127	.19*		.18*	127	.11	119	-.13	.22*	.19*
Marital status	85	-.08	127	.10		.14	127	.24**	119	-.09	.01	.10
Raven score ^b	85	-.18 [†]	127	.29***		.32***	127	.20*	119	-.18 [†]	.30***	.19*
Depression												
Beck depression ^c	85	.16	127	-.05		-.15 [†]	127	-.17 [†]	119	.23*	-.10	-.21*
Major depression ^d	85	.001	127	-.05		-.004	127	-.11	109	.16	.08	-.06
Postpartum												
Depression ^e	85	.02	126	.07		.07	126	.06	108	-.26**	-.06	.03
Anxiety												
State anxiety ^f	85	.06	127	-.13		-.14	127	-.20*	119	.15	-.09	-.06
Trait anxiety ^f	85	.10	127	.05		.000	127	-.03	119	.29**	-.01	-.14
Life stress ^g	62	.12	102	.06		.02	101	-.02	116	.25**	.09	-.10
Marijuana use (days/week)	85	.001	127	-.05		-.003	127	-.01	119	.03	.06	.004
Cigarettes/day	85	.15	127	.05		.11	127	.03	119	.13	.05	-.19*
Infant characteristics												

	Mother-infant interaction									
	During free play					During feeding				
	Infant withdrawal		Maternal sensitivity		Infant responsivity		Quality of interaction		Maternal sensitivity	
	<i>N</i>	<i>r</i>	<i>N</i>	<i>r</i>	<i>N</i>	<i>r</i>	<i>N</i>	<i>r</i>	<i>N</i>	<i>r</i>
Gender ^h	85	.10	127	.03		.05	.10	.10	119	.03
Birth weight	85	-.22*	127	.06		.07	.02	.13	119	.15*
Gestational age	85	-.21 [†]	127	.13		.06	.12	.15	119	.15
Age at visit	85	-.06	127	.03		.02	-.07	-.12	119	-.08
Iron deficiency anemia ⁱ	59	.16	71	-.17		-.14	-.10	-.04	56	.17
Iron deficiency ^j	78	.37***	95	-.25*		-.25*	-.21*	-.10	73	.13

Values are Pearson *r*s.

[†] *p* < .10

* *p* < .05

** *p* < .01

*** *p* < .001

^a Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975).

^b Raven Progressive Matrices (Raven et al., 1996).

^c Beck Depression Inventory (Beck et al., 1996).

^d Structured Clinical Interview for DSM-IV (SCID) Major Depression Module.

^e Edinburgh Postnatal Depression Scale (Cox et al., 1987).

^f State-Trait Anxiety Inventory (Spielberger et al., 1983).

^g Adapted from Holmes and Rahe (1967).

^h 1 = male, 2 = female.

ⁱ Iron deficiency anemia diagnosed if the infant had hemoglobin (Hb) < 10.9 g/L and red cell distribution width (RDW) > 15% plus mean corpuscular volume (MCV) < 70.0 fL or mean corpuscular hemoglobin (MCH) < 23.0 pg.

^J A continuous measure of degree of iron deficiency constructed by averaging z-scores for four indicators of iron deficiency (Hb, MCV, MCH, and RDW). The signs for Hg, MCV, and MCH were reversed so that a higher score indicates a greater degree of deficiency

Table 4
Relation of prenatal alcohol exposure to infant withdrawal, mother-infant interaction, and infant temperament

	N	Average alcohol/day			Drinks/occasion			Frequency		
		At conception	Across pregnancy	At conception	Across pregnancy	At conception	Across pregnancy	At conception	Across pregnancy	At conception
		r	β	r	β	r	β	r	β	r
Infant withdrawal ^a	85	.18 [†]	.15	.19 [†]	.16	.09	.05	.12	.07	.29 ^{**}
Mother-infant interaction										
During free play										
Maternal sensitivity ^b	127	-.11	-.02	-.12 [†]	-.03	-.12 [†]	-.03	-.15 [*]	-.10	-.04
Infant responsivity ^b	127	-.15	-.08 [*]	-.19	-.12 [*]	-.20	-.13 [*]	-.16 [*]	-.14	-.07
Quality of interaction ^c	127	-.07	.06	-.08	.07	-.11	.01	-.09	-.03	.06
During feeding										
Maternal sensitivity ^d	127	-.19 [*]	-.08	-.19 [*]	-.09	-.17 [*]	-.08	-.08	.02	-.17 [*]
Infant EAS Temperament										
Emotionality ^e	105	.16 [†]	.03	.20 [*]	.07	.18 [*]	.07	.16 [*]	.06	.14 [†]
Activity ^f	119	-.26 ^{**}	-.16 [†]	-.24	-.13	-.28 ^{**}	-.20 [*]	-.28 ^{**}	-.23 [*]	-.20 [*]
Sociability ^g	119	-.09	.07	-.11	.09	-.12	-.01	-.16 [*]	-.05	.05
Shyness ^h	119	.04	-.01	.05	.02	.09	.05	.05	.02	-.03

[†] $p < .10$
^{*} $p < .05$
^{**} $p < .01$

^a Confounders: Mother's education, Raven score, birthweight, gestational age.
^b Confounders: Mother's education, socioeconomic status, Raven score.
^c Confounders: Mother's education, socioeconomic status, Raven score, Beck depression score.
^d Confounders: Raven score, Beck depression score, state anxiety, marital status.
^e Confounders: Socioeconomic status, Raven score, life stress, Beck depression score, postpartum depression, trait anxiety.

^f Confounders: Mother's education, socioeconomic status, Raven score, gender.

^g Confounders: Mother's education, Raven score, Beck depression score, pregnancy smoking, birthweight.

^h Confounders: State anxiety, gender.

Table 5

Relation of infant affective measures with 5- and 9-year affective outcomes and IQ

	5-Year EAS						IQ					
	Emotionality		Activity		Sociability		Shyness		Draw-a-Person		5-year	
	N	r	N	r	N	r	N	r	N	r	N	r
Infant withdrawal	60	.18		-.20		-.08		-.02	74	-.26*	80	-.20 [†]
Mother-infant interaction												
During free play												
Maternal sensitivity	101	.06		-.10		-.08		.02	112	.21*	120	.16 [†]
Infant responsiveness	101	-.18 [†]		-.04		-.06		-.04	112	.15	120	.19*
Quality of interaction	101	.01		-.11		-.07		-.03	112	.18*	120	.18*
During feeding												
Maternal sensitivity	100	-.03		-.06		.02		.01	112	.06	120	.15 [†]
Infant EAS temperament												
Emotionality	112	.33***		-.06		.03		.17 [†]	104	.08	113	-.12
Activity	112	-.06		.24		.14		-.17 [†]	104	.03	113	.13
Sociability	112	-.33***		.07		.11		-.23*	104	.02	113	.03
Shyness	112	.23*		-.06		-.00		-.28**	104	-.07	113	-.01

[†] $pp < .10$ * $pp < .05$ ** $pp < .01$ *** $pp < .00$