Neonatal auditory evoked responses are related to perinatal maternal anxiety

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A B S T R A C T

Maternal stress and anxiety during pregnancy are related to negative developmental outcomes for offspring, both physiological and psychological, from the fetal period through early adolescence. This robust relationship is likely to be partly explained by alterations in fetal neurodevelopmental programming, calling for further examination of neurophysiologically-based cognitive markers that may be related to the altered structure–function relationships that contribute to these negative developmental outcomes. The current investigation examined the relationship between perinatal maternal anxiety and neonatal auditory evoked responses (AERs) to mother and stranger voices. Results indicated that neonates of low-anxiety mothers displayed more negative frontal slow wave amplitudes in response to their mother’s voice compared to a female stranger’s voice, while neonates of high-anxiety mothers showed the opposite pattern. These findings suggest that neonates of perinatally anxious mothers may demonstrate neurophysiologically-based differences in attentional allocation. This could represent one pathway to the negative psychological outcomes seen throughout development in offspring of anxious mothers.

1. Introduction

A number of prospective studies have demonstrated associations between maternal anxiety or stress during pregnancy and unfavorable cognitive, behavioral, and emotional outcomes for offspring, with follow-up periods ranging from birth to adolescence (Van den Bergh, Mulder, Mennes, & Glover, 2005). Dysregulation of maternal physiological stress response systems, particularly the hypothalamic–pituitary–adrenal (HPA) axis, during critical periods of fetal development is hypothesized to contribute to this generalized susceptibility to negative psychological outcomes (Huizink, Mulder, & Buitelaar, 2004), with alteration of normal fetal brain development as one potential pathway (O’Connor et al., 2005). Supporting this contention, subjective reports of elevated maternal stress and anxiety during pregnancy are associated with negative neurodevelopmental outcomes across offspring development, including poorer mental and motor development among infants and toddlers (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), attention and concentration difficulties among children (Gutteling et al., 2006; O’Connor, Heron, Golding, Beveridge, & Glover, 2002; Van den Bergh & Marcen, 2004), as well as increased impulsivity and lower intelligence scores (Van den Bergh, Mennes, Oosterlaan et al., 2005), poorer sustained attention (Van den Bergh, Mennes, Stevens et al., 2005) and decreased cognitive control (Mennes, Stiers, Lagae, & Van den Bergh, 2006) among adolescents. These cognitive difficulties may be related to dysfunction of frontal cortex and related neural circuits (Mennes et al., 2006; Van den Bergh, Mennes, Oosterlaan et al., 2005; Van den Bergh, Mennes, Stevens et al., 2005).

In addition to demonstrating a relationship with cognitive functioning, prospective studies have also documented effects of maternal anxiety on the neurophysiological functioning of offspring, with evidence suggesting that these effects may also be long-term. As examples, Field et al. (2003) reported associations between elevated maternal anxiety during the second trimester of pregnancy and lower dopamine and serotonin levels, greater right frontal EEG activation, and lower vagal tone in neonates, while O’Connor et al. (2005) demonstrated that maternal subjective anxiety in late pregnancy was positively associated with salivary cortisol levels among 10-year-old children. In light of this evidence, some have called for examination of specific “marker tasks” and utilization of neuroimaging techniques in order to identify specific “structure–function” relationships that may underlie observed relationships between maternal anxiety or stress during pregnancy and negative psychological outcomes in offspring (e.g., Van den Bergh, Mulder et al., 2005, p. 251). Thus, the present study addresses this need by examining the relationship between perinatal maternal anxiety and neonatal auditory evoked responses (AERs). We are not aware of any published investigations to date that have examined this relationship specifically.

One advantage of using AERs is that they provide excellent temporal resolution in the examination of neural responses to the environment. Moreover, they are particularly useful for studying...
neurocognitive functioning in neonates because they do not require an overt behavioral response. During the first year of life, the AER shows a prominent early positive amplitude peak (often referred to as P2) at about 300 ms. While some investigators have treated this peak as a unitary phenomenon occurring between 150–300 ms (Little, Thomas, & Letterman, 1999) or 150–400 ms (deRegnier et al., 2000; Siddappa et al., 2004), it is more likely to be composed of two separate components, P150 (occurring between 50–250 ms) and P350 (occurring between 250–400 ms; Kushnerenko et al., 2001). Infants also demonstrate a prominent negative peak following this positivity occurring between 350–600 ms (i.e., N450; Kushnerenko et al., 2001). Relatively little is known about the functional significance or the neuroanatomical generators of these peaks in infancy beyond fairly generalized assumptions that they represent obligatory cortical responses related to stimulus detection and processing (Kushenerenko et al., 2001; Little et al., 1999).

These AER components have been examined in the first months of life as indicators of the degree of attentional allocation given to maternal vs. stranger voices. This work stems in part from behavioral data suggesting that newborns are familiar with and prefer their mother’s voice, given that they orient to the sound of their mother’s voice within the first 2 weeks of life (Hammond, 1970), discriminate their mother’s voice from that of strangers (Hepner, Scott, & Shahidullah, 1993), and prefer their mother’s voice to another female voice (Decasper & Fifer, 1980), presumably due to familiarity with her voice developed from intrauterine exposure (Decasper, Lecanuet, Busnel, Granier-Deferre, & Maugeais, 1984; Decasper & Spence, 1986). With respect to AERs, greater attentional allocation to the mother’s voice compared to a female stranger’s voice has reportedly been demonstrated in healthy 4-month-old infants in the form of greater processing negativity after about 350 ms in response to her voice (i.e., lower P350 amplitude, as measured between 250–400 ms, and greater N450 amplitude, as measured between 350–600 ms: Purhonen, Kilpeläinen-Lees, Valkonen-Korhonen, Karhu, & Lehtonen, 2004). These differences were reported to be greatest over frontocentral scalp locations (Fz, Cz, C3 and C4 of the international 10–20 system).

This mother–stranger voice paradigm has also been used to study newborns (38–42 weeks postmenstrual age) of diabetic mothers, a population with increased risk for negative neurodevelopmental outcomes (deRegnier et al., 2000; Siddappa et al., 2004). The investigators examined a P2 component defined as the most positive peak between 150–400 ms (measured at Fz and Cz). For this peak, which was maximal before 300 ms, the mother’s voice elicited a more positive P2 amplitude with a longer latency than did the stranger’s voice in both healthy controls and offspring of diabetic mothers (deRegnier et al., 2000). In another sample composed of only infants of diabetic mothers, however, no P2 amplitude differences were observed in response to the mother’s voice as compared to a stranger’s voice (Siddappa et al., 2004). In both studies, the stranger’s voice elicited greater negative slow wave activity across the waveform than the mother’s voice. This slow wave response was attenuated in newborns of diabetic mothers compared to healthy controls (deRegnier et al., 2000) and in newborns of diabetic mothers with brain iron deficiency compared to those without evidence of such deficiency (Siddappa et al., 2004).

Overall, the above studies of neonate and infant AERs to mother and stranger voices suggest that this paradigm may have utility in detecting neurophysiological dysfunction in offspring related to maternal health during pregnancy. Unfortunately, findings have been somewhat inconsistent with respect to expected AER patterns for the early peaks components. Specifically, Purhonen et al. (2004) found that the mother’s voice elicited a lower amplitude P350, while others showed higher amplitude to the mother’s voice (deRegnier et al., 2000) or no mother vs. stranger-evoked amplitude differences (Siddappa et al., 2004) for P2, an AER component that overlaps with P350. As mentioned previously, the more broadly defined P2 has been reported to consist of both an earlier P150 as well as the later P350 examined by Purhonen et al. (2004). Therefore, examination of these peaks individually would appear to be useful in understanding normal and abnormal AER responses in this paradigm. In addition to considering peaked components, the previous studies also suggest the importance of considering broader slow wave differences potentially related to maternal anxiety.

In summary, offspring of mothers who experience elevated anxiety and stress during pregnancy evidence increased risk for negative neurodevelopmental outcomes across the developmental span. In order to further elucidate potential mechanisms of association between maternal anxiety and negative psychological outcomes for offspring, it becomes important to examine biologically-based markers that may underlie these associations at the earliest stages of life. Newborn AERs to maternal vs. stranger voices may provide such a marker. The current investigation aimed to further explore the newborn AER to mother and stranger voices, as well as to identify potential differences related to maternal anxiety.

2. Methods

2.1. Participants

Subject recruitment and data collection occurred in the maternity ward of a private hospital located in Louisville, Kentucky. A total of 63 mothers consented to participation in the study. Thirteen mother–neonate dyads were excluded because the mother reported tobacco smoking during pregnancy. An additional 11 were excluded because the neonate was restless or distressed during data collection, resulting in termination of the testing session or rejection of the data due to excessive artifacts. Finally, another 11 dyads were excluded due to miscellaneous circumstances including neonate unavailability (e.g. phototherapy or circumcision), a mother’s decision not to continue participation, and an examiner being ill on the day of a scheduled testing session, leaving a final retained sample of 28 mother–neonate dyads. Descriptive statistics are discussed in detail below.

2.2. Materials

2.2.1. Maternal self-report

Mothers completed the Beck Anxiety Inventory (BAI; Beck & Steer, 1990). The BAI is a widely used self-report measure of anxiety severity that consists of 21 symptoms that are rated on a 0–3 point scale, indicating whether the symptoms were “not present” to “severe” over the past week. The BAI demonstrates high internal consistency and test–retest reliability, and differentiates anxiety from depression in clinical and non-clinical samples (Beck & Steer, 1991; Creamer, Foran, & Bell, 1995). The BAI manual (Beck & Steer, 1990) suggests the following classifications based on BAI total score: minimal anxiety (0–7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (26–63), with mean scores for clinically anxious samples falling in the moderate to severe ranges. There has been debate as to whether the BAI better measures panic than more generalized anxiety (Cox, Cohen, Direnfeld, & Swinson, 1996a, 1996b; Steer & Beck, 1996). While BAI scores do tend to be higher in panic disorder with agoraphobia (M = 27.27) and without agoraphobia (M = 28.81), elevated scores are also observed in generalized anxiety disorder (M = 18.83), obsessive–compulsive disorder (M = 21.69) and social phobia (M = 17.77) samples (Beck & Steer, 1990). Further, the BAI is superior to other instruments.
in discriminating anxiety from depression (Creamer et al., 1995) and includes DSM-IV symptoms of both panic and generalized anxiety disorders (Steer & Beck, 1996). Mothers were divided into low-anxiety and high-anxiety groups based on BAI total score as discussed further below.

2.2.2. Maternal voice samples

Mothers’ voices were recorded bedside the evening before neonate testing on an Apple G2 laptop computer, with a Telex M-560 external microphone. Sound Edit 16, Version 2 software was utilized for recording and editing the sound samples. The experimenter modeled pitch, tone, meter, and loudness for enunciation of the stimulus words, “bidu” and “gibu.” The participant was then asked to speak each sound into the microphone repeatedly until a sample of adequate volume, with a sharp onset and offset was obtained. The sound was then edited to a length of 595 ms.

2.2.3. Electroencephalography

Electrical Geodesics’ EGI System 200 (Electrical Geodesics, 2001) was utilized in the collection of EEG data. This system includes a Geodesic Sensor Net consisting of 129 silver/silver chloride plated carbon pellet electrodes, each surrounded by a sponge and set inside a plastic pedestal. Before application, nets were soaked in an electrolyte solution consisting of warm distilled water (1L), powdered potassium chloride (8.5 g), and Johnson’s Baby Shampoo (5 cc). The scalp’s central vertex (Cz) served as a reference against which electrical activity was recorded at the remaining 128 electrode sites. Filters were set to pass frequencies between 0.1 and 30 Hz.

2.3. Procedures

2.3.1. Data collection

Following attainment of written informed consent and recording of voice samples, mothers were provided with self-report questionnaires to be collected by the examiner following neonate testing the next morning. Neonate electrophysiological testing occurred in a quiet room within the nursery without the mother present. Sound levels of the auditory stimuli were set at 80 dB in the 900 ms post-stimulus segment to correct for any baseline variations between electrode channels and trials prior to stimulus onset. Each neonate’s data were averaged within two electrode clusters of interest (frontal and central) and two experimental conditions (mother voice and stranger voice). P150 was measured as the most positive peak between 50–150 ms, P350 was measured as the most positive peak between 250–400 ms, and N450 was measured as the most negative peak between 350–600 ms. Slow wave activity was calculated by averaging the amplitudes across the waveform (stimulus onset to 900 ms) in response to mother and stranger voices, respectively, for each electrode cluster.

2.4. Statistical analyses

Demographic and health-related variables were compared between the low-anxiety and high-anxiety groups using independent samples t-tests and chi-square analyses for continuous and categorical variables respectively. Using anxiety group as a between-subjects factor, repeated measures ANOVAs were conducted for ERP peak amplitude and latency as well as slow wave amplitude, with condition (maternal vs. stranger voice) and electrode cluster (frontal vs. central electrode cluster) serving as within subjects factors. Significant main effects were explored post-hoc with t-tests. Significant three-way interactions were graphed and interpreted based on visual inspection as discussed further below.

3. Results

3.1. Descriptives

Maternal BAI total scores ranged from 2 to 49, with a mean of 15.29 (SD = 11.98), indicating that, on average, mothers reported experiencing mild levels of anxiety. They were divided into low-anxiety and high-anxiety groups based on BAI total score, with 15 (highest level of “mild” anxiety as reported in test manual) serving as the dividing score. This yielded 17 low-anxiety and 11 high-anxiety mothers. BAI total score was significantly higher in the high-anxiety group (M = 25.82, SD = 12.54) than in the low-anxiety group (M = 8.47, SD = 4.27; t(26) = 5.295, p < .001). The mean scores for each of these groups were consistent with expectations for anxiety disordered and non-anxious groups, respectively. As seen in Table 1, low-anxious mothers were slightly older, had delivered more children, and generally had higher income levels. As seen in Table 2, neonates of high-anxious mothers had significantly longer gestational periods although this difference was not clinically significant.

3.2. AER amplitude

A significant condition × electrode cluster × group interaction was observed for both P150 amplitude, F(1, 26) = 4.986, p = .030, and P350 amplitude, F(1, 26) = 4.620, p = .041. For the N450 amplitude, there was a significant main effect for electrode cluster, F(1, 26) = 6.575, p = .016, as N450 was larger for the frontal than the central electrode cluster, t(27) = 2.824, p = .009. The three-way (condition × electrode cluster × group) interaction was only marginally significant for N450, F(1, 26) = 3.142, p = .088. Table 3
presents means and standard deviations for these peaks, demonstrating that neonates of low-anxiety mothers consistently demonstrated more negative frontal AERs in response to their mother's voice compared to the stranger's voice. Neonates of high-anxiety mothers, in contrast, show the opposite pattern for the frontal electrode cluster. This finding is also illustrated in Fig. 1, which presents grand average frontal AERs for each group and condition. No consistent group differences involving the central electrode cluster were evident, as both groups appeared to demonstrate a more negative or equal AER to their mother's voice compared to the stranger's voice.

The highly similar findings across all peaks suggested that a slow wave may better account for the observed findings rather than the individual peaks. Consistent with the peak analyses, a significant three-way (condition × electrode cluster × group) interaction was observed for the slow wave, F(1, 26) = 6.745, p = .015. This effect remained significant when controlling for maternal age, income, and parity, F(1, 23) = 8.658, p = .007. Neonates of low-anxiety mothers exhibited more negative frontal slow waves to their mother's voice compared to the stranger's voice. Again, neonates of high-anxiety mothers showed the opposite pattern as the response to the mother was more positive than the response to the stranger over the frontal cluster (Fig. 2). Using frontal slow wave amplitudes as a covariate, the individual peak effects discussed above were no longer significant.

4. Discussion

Maternal anxiety during pregnancy is associated with negative neurodevelopmental outcomes for offspring, and AERs may provide a useful tool to measure neurophysiologically-based correlates of these developmental abnormalities during early life. The AER paradigm adopted for the current investigation involved measuring neonatal AERs to maternal vs. female stranger voices. Results suggest that neonates whose mother's perinatal anxiety levels fall within normal limits demonstrate more negative frontal slow wave activity to their mother's voice compared to a stranger's voice. This is consistent with a report from Purhonen et al. (2004) that greater processing negativity (lower P350 and greater N450) in response to the mother's voice compared to a stranger's voice reflects the expected greater attentional allocation given to her voice in healthy 4-month-old infants. These authors suggested that such heightened attention to the mother may contribute to "developing and strengthening an emotional tie between the infant and its mother" that is important for healthy development (p. 265).

In contrast to the low-anxiety group, the neonates of high-anxiety mothers did not demonstrate this greater frontal AER negativity to the mother's voice. In fact, they appeared to show the opposite pattern. The implications of this finding are not entirely clear given ambiguities about the nature of infant AERs. Differences in attentional allocation may be implicated which would be important as attentional control processes are crucial to an infant's ability to maintain homeostasis (Wilson & Gottman, 1996). Disruptions in this cognitive mechanism could be related to the developmental difficulties seen in offspring of anxious mothers. Supporting this contention, offspring of prenatally anxious mothers have demonstrated difficulties in attention and self-regulation into adolescence (Van den Bergh, Mennes, Stevens et al., 2005).

It should be noted, however, that other researchers have operationalized similar neonatal AER components as reflecting auditory recognition memory (deRegnier et al., 2000; Siddappa et al., 2004). This highlights the uncertainty that exists around what cognitive or affective processes are implicated in neonatal AER components. There is also inconsistency with regard to directionality of the expected difference between responses to maternal and stranger voices. Our results are consistent with Purhonen et al. (2004) in suggesting that the mother's voice generates a greater negativity, although the other above mentioned group (deRegnier et al., 2000; Siddappa et al., 2004) has presented work to suggest the opposite pattern. Replication is clearly needed to further address this disparity.

In contrast to previous investigations of the impact of maternal anxiety during pregnancy on offspring, the current study utilized a
perinatal rather than a strictly prenatal anxiety measurement. This measurement sampled anxiety during the final week and 1–2 days immediately following the birth. This is not necessarily reflective of the mothers’ baseline levels of anxiety, and longitudinal measurements across the gestational period may have revealed different associations with neonatal AERs. In fact, there has been some speculation in the literature that there are certain critical periods during pregnancy when the influence of maternal anxiety has the greatest impact. For example, Van den Bergh and Marcoen (2004) reported that maternal anxiety at 12–22 weeks gestation was a significant predictor of negative child outcomes while anxiety at 32–40 weeks was not; in contrast, O’Connor et al. (2002) reported that anxiety at 32 weeks gestation was an important predictor (see Van den Bergh, Mulder et al., 2005 for a further review). It is likely that anxiety is fairly stable across the pregnancy period (Heron et al., 2004), and thus the relationship observed in the current study may be due to physiological changes that occurred earlier in the fetal period. Further work is certainly needed to address this area of debate, and the current study suggests the importance of continued consideration of anxiety during later stages of pregnancy.

High-anxiety mothers in the current sample had levels of distress comparable to anxiety-disordered samples. Also interesting, however, they had some important demographic differences when compared to low-anxiety mothers which may have partly explained their level of elevated anxiety. Specifically, they were slightly younger, had delivered fewer children, and had lower household income levels. In addition to being anxiogenic to the mother, these factors could also have a more direct role in impacting the developing fetus. For example, lower socioeconomic status has been identified as an independent risk factor for neonatal encephalopathy in full-term newborns (Blume, Loch, & Li, 2007). While this relationship could be explained by a host of related variables, such as differences in health care access, the current findings support the role of maternal anxiety as an important contributor.

The offspring of high and low-anxiety mothers in the current sample had equivalent outcomes on major obstetric variables, including birth weight, APGAR score, and type of delivery. High-anxiety mothers did have slightly shorter gestational periods, although all pregnancies were within the normal range on this variable. Failure to find more striking differences on such variables could be due to inadequate power or selection criteria which excluded unhealthy neonates. However, the findings are consistent with previous population-based studies which have shown no significant relationship between maternal anxiety and negative delivery outcomes (Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2004; Perkin, Bland, Peacock, & Anderson, 1993).

The current study did not correlate AER variables of interest with objective measures of neonate behavior. A number of other studies in older infants and young children have utilized such methodologies, demonstrating that electrophysiological markers are related to important behavioral constructs such as behavioral inhibition (Bell & Fox, 1992; Buss et al., 2003; Davidson & Fox, 1989; Gunnar & Nelson, 1994). In neonates, greater relative right frontal EEG activity has been positively associated with more disturbed sleep/wake behavior and negatively associated with performance on the Brazelton Neonatal Behavioral Assessment (Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2002). Future investigators may wish to explore associations between such behavioral markers during infancy and differences in the AER components utilized in the current study.

A final limitation of the current study is the relatively small sample size, which may have limited the ability to detect some important group differences. While the findings should therefore be interpreted cautiously until they can be replicated, they do point to potential differences in cognitive processing that are
present at birth as a consequence of elevated maternal anxiety. This adds to a growing body of evidence that elevated maternal anxiety during pregnancy has negative implications for the development of offspring which may be partly due to alterations in neurodevelopment. Further investigation in this realm could improve our understanding of specific pathways to the negative psychological outcomes seen in offspring of anxious mothers. The use of longitudinal designs and the consideration of constitutional–environmental interactions will be important in advancing this literature.

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References


