ARCHIVAL REPORT

Fetal Glucocorticoid Exposure Is Associated with Preadolescent Brain Development

Elyssa Poggi Davis, Curt A. Sandman, Claudia Buss, Deborah A. Wing, and Kevin Head

Background: Glucocorticoids play a critical role in normative regulation of fetal brain development. Exposure to excessive levels may have detrimental consequences and disrupt maturational processes. This may especially be true when synthetic glucocorticoids are administered during the fetal period, as they are to women in preterm labor. This study investigated the consequences for brain development and affective problems of fetal exposure to synthetic glucocorticoids.

Methods: Brain development and affective problems were evaluated in 54 children (56% female), aged 6 to 10, who were full term at birth. Children were recruited into two groups: those with and without fetal exposure to synthetic glucocorticoids. Structural magnetic resonance imaging scans were acquired and cortical thickness was determined. Child affective problems were assessed using the Child Behavior Checklist.

Results: Children in the fetal glucocorticoid exposure group showed significant and bilateral cortical thinning. The largest group differences were in the rostral anterior cingulate cortex (rACC). More than 30% of the rACC was thinner among children with fetal glucocorticoid exposure. Furthermore, children with more affective problems had a thinner left rACC.

Conclusions: Fetal exposure to synthetic glucocorticoids has neurologic consequences that persist for at least 6 to 10 years. Children with fetal glucocorticoid exposure had a thinner cortex primarily in the rACC. Our data indicating that the rACC is associated with affective problems in conjunction with evidence that this region is involved in affective disorders raise the possibility that glucocorticoid-associated neurologic changes increase vulnerability to mental health problems.

Key Words: Development, fetal programming, glucocorticoid, MRI, prenatal, stress

The origins of mental illness often begin early in life (1–4), and it is thought that developmental alterations in brain neuroanatomy underlie vulnerability to psychopathology. Although existing research primarily has focused on postnatal stress exposure (5–9), it is becoming evident that exposure to stress and stress hormones during the prenatal period exert long-lasting consequences on risk for mental health problems, including anxiety and depression (10–14). Because of the rapid neurologic advances during the prenatal period including neurogenesis, migration, cell neuronal differentiation, dendritic arborization, axonal elongation, synapse formation, collateralization, pruning, and myelination (15–18), the fetus is susceptible to environmental influences.

The purpose of this study was to investigate the programming influence of prenatal exposure to excess glucocorticoids on the developing central nervous system during preadolescence. For a number of reasons, glucocorticoids are a candidate for fetal programming of brain development. Glucocorticoids exert a wider array of key metabolic, endocrine, and immune effects on most cells than any other biological ligand (19,20). Furthermore, glucocorticoids pass through the blood–brain barrier, target receptors throughout the central nervous system, and play a central role in normal brain development (21,22). Although glucocorticoids are necessary for normative fetal brain development, exposure to excessive levels may disrupt basic neurodevelopmental processes, and excessive exposures are associated with increased risk for affective problems (12,23). The risk may be even greater when glucocorticoids are administered exogenously, as they are to women in preterm labor, thus exposing the fetus to supraphysiologic levels.

Synthetic glucocorticoids, such as betamethasone, are widely used during pregnancy to prevent respiratory distress syndrome in preterm infants (24,25). The synthetic glucocorticoids used for fetal lung maturation cross the placenta more readily than endogenous maternal glucocorticoids (i.e., cortisol) because they are not metabolized and inactivated by placental enzymes and act directly on the developing fetus (26,27). The pulmonary benefits are undisputed. It is plausible, however, that exposure to excess glucocorticoids has consequences for the developing fetal brain (28,29). Experimental animal research demonstrates that exposure to excess glucocorticoids reduces brain weight, decreases cell proliferation and dendritic branching, disrupts myelination, and alters neural activity across several species including rodents, sheep, and nonhuman primates (30–35). Studies in human neonates indicate that antenatal glucocorticoid treatment is associated with decreased cortical volume and complexity of cortical folding (36,37). Adult human and animal research indicates that limbic and prefrontal regions are particularly affected by excess glucocorticoids because of the abundance of glucocorticoid receptors in these brain regions (9,38–41).

The specific effects of prenatal synthetic glucocorticoid treatment may be observed best among healthy children born at term who are not at risk for the neurologic impairments associated with preterm delivery (42,43). The purpose of the present investigation was to 1) determine the long-term influence of fetal exposure to synthetic glucocorticoids and 2) determine whether cortical changes are associated with affective problems among 6- to 10-year-old preadolescent children.
Methods and Materials

Participants
Participants included 54 children, aged 6 to 10, who were full term at birth and their mothers. Three additional children were recruited into the magnetic resonance imaging (MRI) protocol but not included in this report because adequate imaging data could not be collected due to child refusal or motion artifact. Children were born at either the University of California Irvine Medical Center or Long Beach Memorial Medical Center/Miller Children's Hospital, a community hospital affiliate of the university. The institutional review boards for protection of human subjects at both institutions approved the study protocol. Written and informed consent from the mother and informed assent from the child were obtained before study enrollment.

Inclusion criteria were birth at term (gestational age at birth >37 weeks based on American College of Obstetrics and Gynecology dating criteria) (44), appropriate weight for gestational age at birth, and singleton status. Exclusion criteria were chromosomal or other congenital anomalies (e.g., trisomy 21), postnatal steroid administration and major neonatal illness (e.g., sepsis), maternal preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, maternal drug use, and maternal disorders during pregnancy requiring corticosteroid treatment or thyroid medication. Subjects who met inclusion and exclusion criteria were recruited into two groups: those with and without antenatal exposure to synthetic glucocorticoids. The glucocorticoid group included 18 children (10 girls and 8 boys) whose mothers were at risk for preterm delivery and received the glucocorticoid betamethasone for fetal lung maturation. Beta-methasone is administered in 2 doses (12 mg intramuscularly, 24 h apart). The primary indication for prenatal glucocorticoid administration was preterm labor (72%). Preterm labor was diagnosed by the attending obstetrician based on the following factors: cervical change over time, bloody show (spotting that occurs as the cervix changes shape before or early in labor), cervical effacement and/or dilation, and rupture of membranes. Other associated factors included placenta previa and prolonged premature rupture of membranes. In this cohort, the first dose of betamethasone was given between 24 and 34 weeks’ gestational age (mean gestational age at administration = 29.3 [3.2] weeks) and was between 29 and 107 days before delivery (mean days = 65.1 [21.5]). Although betamethasone is administered because of risk for preterm delivery, 25% to 30% of women who receive glucocorticoid treatment deliver full term (42). Notably, all children in the present investigation were full term at birth. To create a more stable characterization of child brain development among unexposed infants, two children without antenatal glucocorticoids exposure were matched by gestational age at birth and gender to each subject in the prenatal glucocorticoid treated group. Thus, the comparison group consisted of 36 children born at term without prenatal glucocorticoid treatment (20 girls, 16 boys).

None of the participants in the glucocorticoids treatment group or the comparison group had evidence of intraventricular hemorrhage (determined by ultrasound), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period, and all participants had normal neurologic findings (determined by neuroradiologic review of MRI scans), including normal ventricle size, at assessment. Furthermore, at 6 to 10 years of age, no emotional or physical problems were reported in a structured interview using the MacArthur Health and Behavior Questionnaire (45).

MRI Acquisition
Structural MRI scans were acquired on a 3-T Philips Achieva system (Philips, Amsterdam, The Netherlands). To minimize head motion, padding was placed around the head. Ear protection was given to all children. To further increase compliance and reduce motion, children were fitted with headphones and allowed to watch a movie of their choice while in the scanner. Following the scanner calibration and pilot scans, a high-resolution T1 anatomic scan was acquired in the sagittal plane with 1 mm3 isotropic voxel dimensions. An inversion-recovery spoiled gradient recalled acquisition sequence with the following parameters were applied: repetition rate = 11 msec, echo time = 3.3 msec, inversion time = 1100 msec, turbo field echo factor = 192, number of slices: 150, no SENSE (Sensitivity Encoding) acceleration, flip angle = 18°. Acquisition time for this protocol was 7 min.

Image Processing
Cortical surface reconstruction was performed with the FreeSurfer image analysis software suite (http://surfer.nmr.mgh.harvard.edu). Streamlined image processing procedures are initiated by applying intensity normalization before segmentation to minimize errors in identifying the boundaries (49). This is followed by removal of nonbrain tissues (50), and then the images are transformed into the Talairach space for the segmentation of subcortical white matter and subcortical gray matter (51,52). Pial and white matter surfaces were located by finding the highest intensity gradient, which defines the transition from one tissue class to the other (53,54). Once the preprocessing steps were completed, surface inflation was applied to each individual brain (55) and the inflated brains were registered to a spherical atlas. This procedure used individual cortical folding patterns to achieve accurate registration of cortical geometry across subjects (56). Cortical thickness was calculated as the closest distance from the gray matter/white matter surface to the pial surface at each vertex on the tessellated surface (54). Procedures for the measurement of cortical thickness have been

Background Information
Sociodemographic characteristics were determined at the time of study entry by standardized maternal interview. Maternal intellectual performance was determined by the Perceptual Reasoning Scale of the Wechsler Adult Intelligence Scale (46). Maternal depression was evaluated with the Beck Depression Inventory (47). Neonatal and maternal medical characteristics including birth outcome data were determined by medical record abstraction.

Child Behavioral Problems
Child affective problems were measured using the Achenbach System of Empirically Based Assessment, which offers a comprehensive approach to assessing adaptive and maladaptive functioning (48). It is a reliable and valid measure that is widely used in research and clinical practice with children. The parent report form, the Child Behavior Checklist (CBCL), was administered to mothers by a trained interviewer who was directly supervised by a clinical psychologist. The CBCL contains 113 items representing a broad scope of behaviors. It has high test–retest stability and good internal consistency. The Affective Problems subscale was used because it is consistent with the DSM-IV evaluation of affective problems and is a reliable screening instrument (48). The affective problems scale consists of six statements. Responses were made on a 3-point Likert scale ranging from 0 (not true) to 2 (very true). The raw sum scores were transferred to T scores based on the sex-specific reference tables (48).
The number of significant vertices in each lobe. For hemispheric corrections were made as needed.

After false discovery rate (FDR) corrections, the number of vertices was determined in each significant area in each region of the brain. The number of significant vertices for each area was added and divided by the total number of vertices (×100) in that area to provide the percentage of the vertices that were significantly thinner in the glucocorticoid group compared with the comparison group. The same procedure was computed for each region of interest, the number of significant vertices in each lobe. For hemispheric and whole brain percentages, the procedure was the same except the total number of subcortical vertices was subtracted from the total.

**Data Analysis**

Preliminary analyses were performed using χ² and t tests to determine whether sociodemographic (i.e., race/ethnicity, marital marital status, maternal education, and household income), maternal (i.e., intelligence, depression), neonatal (i.e., birth weight, birth order) or child (i.e., age at assessment, affective problems) variables differed by group.

Differences between groups in cortical thickness were analyzed at each node on the cortical surface using the Monte Carlo method. This technique is based on testing statistical significance of clusterwise differences between the two groups for correct labeling of the data against random relabeling (permutations) of the same data. Ten thousand permutations were tested for this study. Spatially normalized cortical thickness maps of each subject were entered into a regression model. Associations were considered to be statistically significant at p < .05 after FDR correction for multiple comparisons as recommended by Genovese and colleagues (60).

Primary regions in which the prenatal glucocorticoid treatment group and the comparison group significantly differed were further evaluated as regions of interest to determine associations with child behavior (affective problems) and timing of glucocorticoid exposure. For each region of interest, the average thickness in millimeters was extracted for each subject from the statistical cortical parcellation file created by FreeSurfer during the segmentation process. This file contains the average thickness in millimeters of the distance between the white matter and the pial surface. Parcellation is based on the Desikan/Killiany Atlas (61).

**Results**

### Demographic and Clinical Data

**Tables 1 and 2** display descriptive information for the study sample. Groups were matched for gestational age at birth and sex. The children in the prenatal glucocorticoid treatment and comparison groups did not significantly differ in birth weight, Apgar scores, race, age at assessment, child affective problems, or in total gray matter volume. Maternal education, marital status, household income, intelligence and depression did not significantly differ between the treatment and comparison groups.

### Is Prenatal Glucocorticoid Treatment Associated with Cortical Thickness in Preadolescent Children?

Widespread and predominantly bilateral differences in cortical thickness were observed between groups. Four percent of the cortex was thinner among children who were exposed to synthetic glucocorticoids during the fetal period. Regionally specific consequences of fetal exposure to synthetic glucocorticoids were

**Table 2. Descriptive Information for Mothers in the Study Sample**

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoid Treatment Group</th>
<th>Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age at Assessment (Years)</td>
<td>36.9 (6.2)</td>
<td>36.3 (6.4)</td>
</tr>
<tr>
<td>Range: 26.1–48.8</td>
<td>Range: 24.4–48.8</td>
<td></td>
</tr>
<tr>
<td>Married or Cohabitating (%)</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary, elementary, or middle school</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>High school or equivalent</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Associates or vocational</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Annual Household Income (%)</td>
<td>$0–$30,000</td>
<td>6</td>
</tr>
<tr>
<td>$30,001–$60,000</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>$60,001–$100,000</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Over $100,000</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Beck Depression Inventory Score</td>
<td>7.7 (6.0)</td>
<td>8.1 (8.7)</td>
</tr>
<tr>
<td>Range: 0–19</td>
<td>Range: 0–32</td>
<td></td>
</tr>
<tr>
<td>WAIS: POI Index Score</td>
<td>97.8 (13.7)</td>
<td>95.4 (16.0)</td>
</tr>
</tbody>
</table>

Study groups did not significantly differ on any of these measures. All ps > .2.

POI, Perceptual Organization Index; WAIS, Wechsler Adult Intelligence Scale.
observed (Table 3). Regions where group differences achieved statistical significance ($p < .05$) after FDR correction are shown in Figure 1 (red overlays).

The most prominent group differences were seen bilaterally in areas of the cingulate cortex including the rostral and caudal anterior cingulate, the isthmus cingulate, and the left posterior cingulate. The cortex was additionally significantly thinner in frontal regions including the superior frontal cortex, the lateral orbital frontal cortex, and the precentral gyrus as well as the right medial orbital frontal cortex and rostral and caudal middle frontal cortex (dorsolateral prefrontal cortex), and the left pars triangularis and parsopercularis. Areas of significant bilateral cortical thinness among the glucocorticoid-exposed group were observed in the superior parietal cortex. Unilateral regions of thinning were observed in the left insula, left supramarginal gyrus, and the left transverse temporal cortex as well as the right inferior temporal cortex. As shown in Table 3 and Figure 2, by far the area most strongly associated with prenatal glucocorticoid treatment was the rostral anterior cingulate cortex (rACC). More than 30% of the rACC was thinner in the glucocorticoid group. Furthermore, the magnitude of the effect was substantial; the rACC was 8% and 9% thinner for the left and right hemisphere, respectively. We investigated this region of interest to determine whether thickness was associated with affective problems or timing of exposure. Although groups did not differ in affective problems, it is plausible that thickness of the rACC is associated with affective problems, suggesting that reduced rACC thickness is a prodromal risk factor for affective problems.

**Is Thickness of the rACC Associated with Affective Problems?**

Hierarchical linear regression, covarying group status, indicates that a thinner left rACC cortex is significantly associated with a higher level of child affective problems; $\Delta R^2 = .12$, $\beta = -.36$, $t = -2.7$, $p < .01$. As shown in Figure 3, these data suggest that thinning in this region is associated with risk for affective problems. The association was not significant for the right rACC; $\Delta R^2 = .003$, $\beta = .06$, $t = .4$, $p = .7$. Evaluation of the association between rACC and affective problems within each group indicated a significant association within the comparison group ($r_{36} = -.45$, $p < .01$) but not for the glucocorticoid group ($r_{18} = -.1$, ns).

**Is Timing of Exposure Associated with Cortical Thickness?**

Within the range of glucocorticoid administration (24–34 gestational weeks), timing of administration was not significantly associated with thickness of the rACC ($p > .1$).

**Discussion**

To the best of our knowledge, these data provide the first evidence that prenatal treatment with glucocorticoids alters the trajectory of fetal brain development with neurologic consequences that persist into the preadolescent period. Children who were exposed as fetuses to glucocorticoid treatment have significantly thinner cortices, primarily in the rACC, a region that plays a critical role in stress and emotional regulation (62,63). Not only is more than 30% of the rACC thinner among children with fetal exposure to glucocorticoid treatment, but the magnitude of the effect is also substantial. The rACC is 8% to 9% thinner among glucocorticoid-treated children. The possible clinical significance of this association is underscored by the observation that there is a 10% to 14% reduction in the rACC among children with depressive symptomatology (64). Consistent with the possibility that these neurologic changes may indicate prodromal risk for mental health problems, we show that a thinner rACC predicts increased child affective problems. Notably, the significant associations are observed among children who are healthy and born at term, and these findings cannot be explained by sociodemographic (income or education) or maternal (depression, IQ) factors.

Recent studies provide evidence that fetal exposure to elevated levels of glucocorticoids has consequences for stress and emotional regulation including hypothalamic-pituitary-adrenal (HPA) axis dysregulation (65–67), fearful temperament...
(68–70), anxiety (12), and affective problems (23) during infancy and childhood. This study indicates fetal glucocorticoid exposure alters the development of the ACC and represents one pathway through which fetal stress exposures may contribute to affective problems. Our finding that the ACC is particularly vulnerable is consistent with several lines of evidence. First, the ACC is rich in glucocorticoid receptors and susceptible to damage resulting from excess exposure (71–73). Second, postnatal exposure to stress or trauma is associated with a decrease in ACC volume (5,74,75). Third, birth weight is associated with thickness of the rACC indicating that development of this region is affected by fetal experiences (76).

Because of the massive developmental changes occurring during gestation, the fetal brain is vulnerable to exposures including elevated glucocorticoids (29), stress (77), infection (78,79), poor nutrition (80), and environmental toxins (81). Although glucocorticoids play an organizational role in normative fetal maturational processes (21,22,82), exposure to excessive levels of glucocorticoids during sensitive periods has neurotoxic effects and may lead to dysfunctional developmental trajectories (23). Rodent studies have documented that prenatal glucocorticoid exposure affects postnatal brain cell proliferation and levels of glucocorticoid receptor messenger RNA (mRNA) (83–85). In sheep, antenatal glucocorticoid treatment leads to acute changes in neuronal activity (86,87), decreased cerebral blood flow (88), disrupted myelination of white matter tracts (89), and decreased brain weight persisting through adulthood (90), with repeated doses having a more profound effect (89,91). Primate studies provide further evidence for a persisting influence of prenatal glucocorticoid treatment on the brain (92). A single course of betamethasone decreased expression of neuronal cytoskeletal proteins and of the presynaptic marker synaptophysin, proteins that are necessary for brain development and neuronal functioning (93). The few human studies of brain development have evaluated the fetus or neonate and have shown that fetal exposure to glucocorticoid administration is associated with reduced neonatal cerebral cortical gray matter volume among preterm infants (36), decreased complexity of cortical folding and brain surface area among late preterm infants (37), and acute changes in fetal cortical functioning between 29 and 34 gestational weeks (94).

Our findings described here extend the existing literature by evaluating children born healthy and full term and exposed to a single course of betamethasone and show that fetal glucocorticoid treatment is associated with cortical thinning that persists until at least 6 to 10 years of age. We have focused on cortical thickness because it has been suggested that cortical thickness provides an index of the integrity of cortical cytoarchitecture (95) and as such may be more sensitive to neurodegenerative processes than cortical volumes (96,97). Thinning of the cerebral cortex during the preadolescent period is a normative developmental process likely associated with synaptic pruning (98). Because age did not significantly differ between groups and was statistically covaried in the present analyses, it is unlikely that cortical thinness observed here is related to maturational processes. Thus, the present findings raise the possibility that exposure to antenatal glucocorticoids is associated with an acceleration of this maturational process. Alternatively, it is plausible that these children already had a thinner cortex even before the synaptic pruning associated with preadolescence and adolescence. These possibilities are consistent with rodent research demonstrating that glucocorticoid exposure causes morphologic rearrangements in the apical dendrites in the ACC (71), which may underlie the observed associations with cortical thickness.

The ACC, and most predominantly the rACC, has been associated with mood disorders including depression, anxiety, and bipolar disorders (99–101) as well as HPA axis dysregulation.
Implications

state, or socioeconomic status. Demographic factors including maternal intelligence, psychological group differences are not observed on a number of clinical and treatment and cortical development. As illustrated in Table 1, two groups contributed to the association between glucocorticoid (e.g., prenatal maternal stress hormones) that differed between the differences in physiologic regulation associated with shortened children born at term and thus cannot be attributed to illness or mask the consequences of glucocorticoids (66). In our investiga-
delays. It is plausible that risk factors associated with prematurity were quite ill and thus were already at risk for developmental
full term. Existing published research is complicated by the fact current investigation is the inclusion of children who were born preterm, it is not ethical to randomly assign women in assigned to treatment, and thus it is plausible that preexisting fetal
benefits of glucocorticoid treatment for survival among children differences contribute to the current observations. Because of the
advantages. The current findings indicate that prenatal glucocorticoids shape the construction of the fetal nervous system with conse-
quences for the developing brain that persist into the preadoles-
cent period.

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Strengths and Limitations

A primary limitation is that participants were not randomly assigned to treatment, and thus it is plausible that preexisting fetal differences contribute to the current observations. Because of the benefits of glucocorticoid treatment for survival among children born preterm, it is not ethical to randomly assign women in preterm labor to glucocorticoid treatment. A strength of the current investigation is the inclusion of children who were born full term. Existing published research is complicated by the fact that studies of children who have been exposed to glucocorticoid treatment primarily include children born preterm, many of whom were quite ill and thus were already at risk for developmental delays. It is plausible that risk factors associated with prematurity mask the consequences of glucocorticoids (66). In our investiga-
tion, the observed association between fetal exposure to glucocorticoids and child brain development were observed among children born at term and thus cannot be attributed to illness or differences in physiologic regulation associated with shortened gestation. It is plausible, however, that fetal or maternal conditions (e.g., prenatal maternal stress hormones) that differed between the two groups contributed to the association between glucocorticoid treatment and cortical development. As illustrated in Table 1, group differences are not observed on a number of clinical and demographic factors including maternal intelligence, psychological state, or socioeconomic status.

Implications

There is growing recognition that early experience is a primary factor contributing to mental illness. It has recently been estimated that exposure to early adversity may explain more than 30% of the risk for developing mental illness (4). Glucocorticoids are powerful regulators of neural differentiation and maturation and may play a salient role in neurodevelopment and risk for mental disease. Furthermore, recent animal work has demonstrated that prenatal exposure to elevated glucocorticoids results in epigenetic changes with both life span and intergenerational consequences (104–107). We show that prenatal administration of glucocorticoids results in a pattern of cortical thinning that may be an indication of increased vulnerability to mental impairments. Regions such as the ACC that are associated with prenatal glucocorticoid treatment are ones that are implicated in risk for mental health problems, including affective problems. Greater understanding of the developmental origins of mental illness is a critical step for the development of new diagnostic methods and improved treatments. The current findings indicate that prenatal glucocorticoids shape the construction of the fetal nervous system with consequences for the developing brain that persist into the preadolescent period.

The authors report no biomedical financial interests or potential conflicts of interest.

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