First Trimester Dexamethasone Treatment Is Not Associated With Alteration in Resting-state Connectivity at Adolescent or Adult Age

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Abstract

Context: Prenatal treatment with dexamethasone (DEX) has been used to prevent virilization in females at risk of congenital adrenal hyperplasia (CAH). Both affected and unaffected girls, as well boys, are treated until the genotype and sex of the fetus is known (gestational weeks 10-12). After that, only affected girls are treated until term. Exposure to a high synthetic glucocorticoid dosage may alter the developmental trajectory of the brain, with alterations in resting-state functional connectivity of the brain at adult age.

Objective: To investigate resting-state functional connectivity in subjects at risk of having CAH, exposed to DEX treatment during the first trimester of fetal life, both in the whole brain and in 3 regions of interest (amygdala, hippocampus, and superior frontal gyrus).

Design, Setting, and Participants: Eighteen participants (8 females) at risk of having CAH, exposed to DEX treatment, and 38 controls (24 females), age range 16 to 26 years, from a single research institute, underwent functional magnetic resonance imaging of the brain during rest.

Results: We did not observe any differences in functional connectivity during rest, either in the whole brain nor in seed-based connectivity analyses at this adolescent and young adult age.

Conclusions: Our results are reassuring; however, future studies on larger samples and with more sensitive methodologies are needed to confirm these findings.

Key Words: brain function, cognition, dexamethasone, prenatal treatment, resting state

Abbreviations: CAH, congenital adrenal hyperplasia; DEX, dexamethasone; GC, glucocorticoid; ICA, independent component analyses; MRI, magnetic resonance imaging; RSN, resting-state network; WAIS, Wechsler Adult Intelligence Scale.

Prenatal treatment with the synthetic glucocorticoid (GC) dexamethasone (DEX) has been offered since the mid-1980s to mothers at risk of carrying a fetus with classic congenital adrenal hyperplasia (CAH). Both affected and unaffected girls, as well boys, are treated until the genotype and sex of the fetus is known (gestational weeks 10-12). After that, only affected girls are treated until term. Exposure to a high synthetic glucocorticoid dosage may alter the developmental trajectory of the brain, with alterations in resting-state functional connectivity of the brain at adult age.

Foetal virilization starts during weeks 6 and 7 after conception; hence, to be effective, the treatment needs to be initiated before week 7 when the genotype or sex of the fetus is not yet known (1,3). Synthetic DEX is not inactivated by placental 11β-hydroxysteroid dehydrogenase, and so all the fetuses affected and unaffected by CAH will be exposed to a high dose of GC (about 60 times higher than usual) during embryonic life, until the results of the genetic diagnosis are available (4). The treatment will be stopped in healthy fetuses and in CAH-affected boys, whereas affected girls will be treated until term (1 in 8 fetuses). However, although the treatment is proven to be efficacious, ethical implications and safety issues are a major concern (5).

Glucocorticoids play an important role in normative fetal development, but exposure to high GC levels already in utero may affect fetal programming, altering the development trajectory of the brain, potentially affecting both the structure and the functional organization of the brain, with consequent long-term adverse health outcomes related to cognition, behavior, and mood regulation (6-10).

Accumulating evidence suggests that higher GC doses may alter neurogenesis, gliogenesis, synaptogenesis, as well as cell proliferation and dendritic proliferation in key regions of the brain with a high density of glucocorticoid receptors, in particular the medial prefrontal cortex, hippocampus, and amygdala, among others. These regions are important for executive functioning, learning and memory, and emotional regulation respectively, and high GC doses may lead to changes in their structural and functional connectivity (11-13).

Depending on study design, cohort size and age, as well as type, dose, and time of medication, and stage of pregnancy, results on the effects of treatment with synthetic GC
or maternal stress during prenatal life, on the structure and function of the brain, as well as on cognition and behavior are contradictory. Moreover, all the previous research has focused on the exposure to synthetic GC or maternal stress during the second and third trimesters, reporting alterations in functional connectivity in the amygdala, amygdala, and hippocampal volume, as well as decreased gray matter density in children and adolescents (14-18).

Studies evaluating the long-term effects of treatment during the first trimester on brain, cognition and behavior are scarce. Recently, our group has started to address the long-term effects because the treated children are now reaching adult age. In our previous studies, in a cohort of healthy children and adolescents (7-17 years) at risk of CAH, prenatally treated with DEX, compared with population controls, we observed impairments in verbal working memory in DEX-treated children (19), which was later confirmed to be more pronounced in first trimester DEX-treated girls (20). However, at adult age, we found a significant improvement in executive functions, suggesting a compensation mechanism or catch-up during development (21). Interestingly, when investigating the effect of prenatal treatment on brain structure in 18 participants, at risk of CAH but not having CAH and prenatally treated with DEX (16-33 years), we did find alterations in gray matter and white matter microstructure. In particular, we observed an enlargement of the amygdala (bilateral) as well as of the left superior frontal gyrus, in addition to impairments of white matter microstructure in major fiber tracts (22). Despite these structural alterations, DEX-treated subjects performed equally well on cognitive tasks and did not show any impairments in behavior (eg, symptoms of anxiety and depression), compared with the control group at adolescent and young adult age (22). Moreover, when we investigated functional connectivity in the brain, in the same cohort we did not identify any differences in brain activity during working memory performance (23). These findings point at compensatory mechanisms because, despite changes in structures of the brain, prenatally DEX-treated healthy subjects are able to achieve normal brain activity during task performance and normal cognitive functions.

To our knowledge, there are no studies assessing resting-state functional connectivity in individuals treated with glucocorticoids during early fetal life. Here we examine resting-state functional connectivity in a group of adolescent and young adults prenatally treated with DEX during the first trimester, but not having CAH, and compare them with population controls. First, we aim to assess whole-brain resting-state functional connectivity. Further, based on our previous findings of enlargement of the amygdala and increased volume in the left superior frontal gyrus, as well as evidence from the literature of a high GC receptor density in the hippocampus (24), we hypothesize that functional connectivity during rest might be altered in the amygdala, superior frontal gyrus, and hippocampus. Both data-driven, independent component analysis (ICA) and seed-based correlation analysis were conducted.

Methods

Participants

The recruitment process has been described elsewhere (21, 25). The participants were selected from a larger longitudinal study (PREDEX study) investigating short- and long-term effects of pre- and postnatal treatment with GCs in patients with CAH (20, 22, 25, 26) and included only participants not having CAH who had received prenatal DEX treatment during the first trimester (range start DEX, gestational weeks (GWs) 5-9; range stop DEX, gestational weeks (GWs) 10-22; mean duration DEX, 6 weeks [range, 1.5-14 weeks]) and nontreated control individuals from the general population. All the control participants, recruited from the general Swedish population, were matched for age and sex to the DEX cohort and lived in the Stockholm County area. The present analyses were performed on n = 18 (8 female) DEX-treated participants, mean age = 20.4 years; age range, 16.3 to 26.4 years; and n = 30 (24 female) controls, mean age = 20.3 years (2.7); age range, 16.7 to 26.4 years. The study was approved by the Regional Ethics Committee of Karolinska Institutet and Stockholm (dnr. 99-153 and 2011/1764-32), and all participants and parents of children younger than 18 years gave their informed consent before study inclusion.

Procedure

The study procedure has been described previously in detail (21, 23, 27). Briefly, the participants completed neuropsychological tests and, on a separate day (mean difference 263 days, range 0-800 days), a 70-minute magnetic resonance imaging (MRI) brain scan on a 3T MR scanner (Discovery MR750, General Electric) with an 8-channel head coil. Resting-state functional MRI data were used in the present study. The acquisition time for the resting-state functional MRI was 8 minutes. During the resting-state functional MRI, participants were instructed to keep their eyes closed for the whole sequence.

A well-being self-report estimation based on a 10-point visual analogue scale was obtained for each participant after the scanning. In addition, a screening questionnaire regarding lifestyle and health-related problems was filled out by the participants. All participants were healthy based on this self-reported lifestyle and health-related problems questionnaire.

Neuropsychological tests included verbal and nonverbal intelligence (Wechsler Adult Intelligence Scale (WAIS)-IV Vocabulary and WAIS-IV Matrices (28), executive functions and working memory performance (WAIS-IV Digit Span (28) and Span Board Test (29)), learning and memory (Wechsler Memory Scale-III List Learning Test (29)), and processing speed and interference (Wechsler Memory Scale-III Coding (29) and the Stroop Task (30)). Self-rated questionnaires were used for the assessment of executive functioning (Barkley Deficit in Executive Functioning Scale–Short Form (31)) and depressive and anxiety symptoms (Hospital Anxiety and Depression Scale (32, 33) and Liebowitz Social Anxiety Scale–Self-Report (34)).

Nonimaging Statistics

Demographic data and assessment of cognitive functions and behavior

The variables we studied were tested for normality and homogeneity of variance before each analysis. Analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA). For the demographic data, a 1-way ANOVA was conducted to compare DEX-treated participants with controls in terms of age. For the remaining variables, a non-parametric test (Mann-Whitney) was performed to compare DEX treated subjects to controls.

Results are reported as median (interquartile range), unless otherwise indicated. Group differences were considered to be significant at 𝑝 < 0.05.
Resting-state functional MRI data analysis

Data preprocessing. Resting-state functional MRI data were preprocessed using FMRIB’s Software Libraries version 5.0.11 (FMRIB Laboratory, University of Oxford, England, UK) (35). Briefly, the preprocessing included co-registration of each participant’s structural image with the functional image and head motion correction using MCFLIRT (36), slice timing correction, and brain extraction using a brain extraction tool (37), and finally, spatial smoothing with a Gaussian kernel of 5 mm full width.

Each participant’s functional images were registered to the participant’s structural images, using the FMRIBs Linear Image Registration Tool (36, 38) and to the standard space (MNI152) images using nonlinear registration with a warp resolution of 10 mm.

After data preprocessing, the “aggressive” option of the ICA-based automatic removal of motion artifacts was used to identify and remove motion artifacts from the time series (39, 40). ICA-automatic removal of motion artifacts is a robust strategy not requiring a study-specific training dataset. Motion-related components are automatically detected and removed from the initial data set through an ordinary least-squares regression (39).

Independent component analysis. The cleaned individual data of resting state was fed into the spatial ICA to extract resting-state networks. ICA was performed using MELODIC v 3.15 software (FSL, Oxford, UK) (41).

First, we performed ICA separately for each of the 2 groups (participants prenatally treated and controls) to map the resting state networks (RSNs). The number of independent components was set to 60.

We then classified the RSNs based on their spatial similarity to the functional networks described in healthy people (42) by visually inspecting the aggregate spatial maps, time courses, and the power spectrum. Next, the entire group of the preprocessed data, consisting of 56 participants, was concatenated and entered into an ICA group to identify common functional connectivity patterns for the whole cohort.

Dual regression analysis

Dual regression was used to regress the obtained group ICA components back into the individual participant’s space for all 56 participants (41). Next, group comparisons were performed using the FSL randomize tool (43) with 5000 permutations to identify differences in resting-state connectivity in the identified networks between DEX-treated participants and controls, after controlling for age and sex. Significant clusters were identified with threshold-free cluster enhancement with a significance threshold of \( P < 0.05 \) (43).

Seed-based connectivity analyses

For seed-based connectivity analysis, we chose brain regions based on the findings of our structural brain study (22) and on previous evidence on the vulnerability to high GC dosages. Specifically, we identified 3 different regions, amygdala, hippocampus, and superior frontal gyrus, using the Harvard-Oxford cortical Atlas (FSL) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and we created right and left masks for each region. Finally, the time-series of these 3 regions were modeled with GLM analysis using the FMRI Expert Analysis Tool (44, 45) to estimate the region of interest connectivity maps for each subject. These maps represent the functional connectivity between the region of interest and the rest of the brain. For the group-level comparisons, age and sex were used as covariates. Group-level maps were clustered using standard values of \( Z = 2.3 \) and FWE \( P < 0.05 \).

Results

Characteristics of the Study Group and Assessment of Cognition and Behavior

There were no group differences in age, height, weight, body mass index, and overall well-being between DEX-treated participants and control participants at the time of scanning (Table 1).

For the neuropsychological assessment, we did not identify any differences between groups, either in cognition (Table 2) nor in behavior (Table 3).

Table 1. Characteristics of the first trimester DEX-treated cohort and population controls

|                | DEX (n = 18) | Control (n = 38) | DEX vs C |
|----------------|-------------|-----------------|---------|
|                | Female (n = 8) | Male (n = 10) | Female (n = 24) | Male (n = 14) | P values |
| Age, mean (SD) | 20.6 (2.6)   | 20.9 (2.8)      | 20.2 (2.4)    | 21.0 (3.0)    | 0.697*   |
| Subject education\(^a\) | 2.00 (2.00, 2.00) | 2.00 (2.00, 2.00) | 2.00 (1.00, 2.00) | 2.00 (1.75, 2.00) | 0.313 |
| Well-being\(^b\)   | 6.60 (4.45, 7.77) | 7.50 (6.05, 8.15) | 7.50 (7.00, 8.00) | 7.35 (6.20, 8.32) | 0.174 |
| Height (cm)       | 167.80 (160.15, 172.97) | 183.40 (174.00, 187.35) | 169.50 (165.00, 174.12) | 181.00 (177.25, 184.37) | 0.703 |
| Weight (kg)       | 56.05 (52.72, 61.90) | 78.50 (71.60, 83.15) | 64.50 (21.63, 25.75) | 75.00 (68.50, 92.75) | 0.375 |
| BMI              | 19.93 (19.41, 20.91) | 22.81 (21.52, 26.90) | 21.63 (20.53, 25.75) | 23.67 (20.63, 27.10) | 0.364 |
| Alcohol\(^d\)     | 1.00 (0.00, 1.75) | 1.00 (0.00, 1.50) | 7.50 (7.00, 8.00) | 1.00 (0.00, 2.00) | 0.838 |
| Drugs\(^e\)       | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 1.000 |
| Smoking\(^f\)     | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.00) | 0.703 |

Values are displayed as mean (SD) for age and median (interquartile range) for nonparametric tests. ANOVA was used for the comparison of age between groups. For all other variables, Mann-Whitney \( U \) tests, exact statistics were used. \( P \) values are reported for the comparison DEX-treated vs controls. Abbreviations: BMI, body mass index; C, control; DEX, dexamethasone.

\(^a\)Level of education level: 1-3 (1: basic, 2: high school, 3: college).

\(^b\)General well-being, according to a 10-point visual analogue scale.

\(^c\)Alcohol consumption (number of times alcohol is consumed per week).

\(^d\)Drug consumption (yes/no).

\(^e\)Smoking behavior (yes/no).

\(^f\)F(1,36) = 12.7.
We did not observe any differences in resting-state functional connectivity between any of the chosen seed regions (amygdala, superior frontal gyrus, and hippocampus) and the rest of the brain in DEX-treated participants compared with the control group. The obtained RSNs included visual (pole and medial), motor leg-hand and motor-face regions, cerebellum, auditory/language, dorsal attention, salience, default mode (medial prefrontal cortex and posterior cingulate cortex, frontoparietal (executive), and basal-ganglia networks (Fig. 1).

Dual Regression Analysis
We did not identify any differences in resting state functional connectivity in any of the networks between the DEX-treated participants and the control group.

Seed-based Connectivity Analyses
We did not observe any differences in resting-state functional connectivity between any of the chosen seed regions (amygdala, superior frontal gyrus, and hippocampus) and the rest of the brain in DEX-treated participants compared with the control group.

Discussion
In this study, we examined, for the first time, resting-state functional connectivity in adolescent and young adult participants who were at risk of having CAH, and therefore had been treated with the synthetic glucocorticoid dexamethasone during the first trimester of prenatal life. Compared with age-matched control subjects, we did not observe any differences in resting-state functional connectivity in DEX-treated subjects, neither in the whole brain nor between 3 a priori specified regions of interest and the rest of the brain, that is, the amygdala, hippocampus, and superior frontal gyrus. There were no differences in cognitive performance or symptoms of depression or anxiety either.
Previous research from our group showed impairments in verbal working memory in first trimester DEX-treated participants when they were children and adolescents (7-17 years), with girls being more affected than boys (20). At adult age, however, there was a significant improvement in performance, and we did not observe any differences between our DEX-treated group and controls (21). Although this may partly have been caused by the smaller sample size in the

Figure 1. Resting-state functional networks. (A) Visual (pole), (B) visual (medial), (C) motor leg-hand, (D) motor face regions, (E) cerebellum, (F) auditory/language, (G) dorsal attention, (H) Salience network, (I) Default Mode Network (mPFC), (J) Default Mode Network (PCC), (K) fronto-parietal (executive network), and (L) basal-ganglia.
adult cohort, it does suggest that the children catch up in terms of cognitive abilities when they grow up. Interestingly, we did find differences in structure of the brain in the adult cohort. DEX-treated subjects had increased volume of the bilateral amygdala, larger surface area of the left superior frontal gyrus, and widespread alterations in white matter microstructure, pointing at impairments of white matter in the major fiber tracts (22). In addition, white matter microstructure estimates correlated with methylation of the FKBP5 gene, a co-chaperone of the GC receptor that is involved in hypothalamic-pituitary-adrenal axis regulation (22). These findings point at a prenatal programming effect of high GC levels during the first trimester on the structure of the brain. Given the generally good cognitive and behavioral performance, in combination with altered brain structure, we had expected to find compensatory functional connectivity alterations in the DEX-treated group. However, we did not find any such changes either in the whole brain or in the regions where we found a structural difference.

One possible explanation for this lack of difference is that the structural alterations that we observed are the expression of an adaptive mechanism of the brain that has led to normalized brain function and connectivity patterns. Indeed, our finding of a lack of difference in resting-state functional connectivity is in line with the lack of difference in brain activity during verbal and visuospatial working memory tasks in the same cohort of DEX-treated subjects at adult age (23). Alternatively, other mechanisms may be at play and contribute to compensatory effects eventually leading to functional activity and connectivity similar to that of controls, despite structural changes.

The mechanisms underlying these changes are not yet known. Structural networks develop earlier than functional networks and already at birth they present an adult-like topological organization. On the contrary, functional networks exhibit more dramatic changes during development (47). Potentially, very early GC excess affects mostly brain structure, as opposed to function, in humans, while GC exposure during second and third trimester of pregnancy may result in changes in structural (15, 48) and functional connectivity (49), as well as affecting cognition and behavior (15, 50, 51). However, we cannot rule out that our methodology is not sensitive enough to detect differences in brain organization and functions. Cognitive performance depends on the interaction between different brain networks (52). The integrity of these networks may be perceived from the degree of functional connectivity between different brain regions, which underlie an exchange of information between different networks (52). These cognitive networks are also active at rest, and differences in activity can be found between patients and controls (53). More sensitive methods, such as graph analyses, may be better suited to find differences in whole brain organization as a result of prenatal GC excess, for example by assessing network segregation and integration (54, 55).

Some networks play an important role in the integration of complex cognitive functions. In general, networks are characterized by “nodes” that communicate with different subregions of the brain (56). Highly connected nodes, defined as “hubs,” have a higher cognitive demand and are potentially more sensitive to early prenatal GC disturbances (57). Indeed, subjects prenatally treated with DEX, and thus exposed to high GC dosages, may follow an altered developmental trajectory of brain network maturation and organization. Future studies are needed to assess these aspects of brain organization in DEX-treated subjects.

Careful assessment of the effects of DEX-treatment in the context of CAH is important to determine treatment safety. Although the current results are promising, we urge for more detailed investigation, potentially in larger samples.

Limitations
The important strength of this study is the unique cohort that we were able to follow prospectively. A limitation of this study is the low power due to the relatively small sample size, which may have prevented detection of potential differences in functional connectivity and behaviour. Because of sample size, we could not perform a more detailed evaluation of sex-specific differences in functional connectivity. Another limitation might be related to the used methodology that may be not sensitive enough to detect differences in brain organization and functions.

Larger groups and different methodologies are needed to investigate the impact of prenatal DEX treatment during the first trimester on resting-state functional connectivity in subjects at risk of CAH.

Conclusion
Despite alterations in brain structure at adolescent and young adult age, and cognitive impairments during childhood and adolescence, we could not identify any effect of prenatal DEX treatment on resting-state functional connectivity at adolescent and adult age by using resting-state functional connectivity, group-independent component analysis, and seed region analysis. These results are reassuring, however, future studies on larger samples and with more sensitive methodologies are needed to confirm these findings.

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Disclosures
The authors have nothing to disclose.

Data Availability
The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
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