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Pituitary lacks sexual dimorphism and displays reduced signal intensity on T1-weighted MRI in adolescents with histories of heavy prenatal alcohol exposure

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ABSTRACT

Prenatal alcohol exposure can interfere with endocrine function and have sex-specific effects on behavior. Disrupted development of the pituitary gland, which has been observed in rodent studies, may account for some of these effects. To determine if gestational exposure to alcohol produces measureable changes in the pituitary in human adolescents, we manually traced the pituitary in T1-weighted structural magnetic resonance images (MRI) from adolescents with (15 males, 11 females) and without (16 males, 11 females) heavy prenatal alcohol exposure. Pituitary gland volume and maximum signal intensity were examined for group differences. Control female adolescents presented with significantly greater pituitary volume compared to males, as has been previously reported. However, this sexual dimorphism was absent in adolescents with histories of prenatal alcohol exposure. Alcohol-exposed adolescents, regardless of sex, demonstrated reduced pituitary maximum signal intensity compared to controls. The lack of a sex difference in pituitary volumes within the alcohol-exposed group suggests such exposure may interfere with adolescent typical sexual dimorphism of the pituitary. Signal intensity in the posterior pituitary may reflect vasopressin storage. Our findings suggest vasopressin activity should be evaluated in alcohol-exposed adolescents.

1. Introduction

There are well-documented detrimental effects of prenatal alcohol exposure on embryonic and fetal development. Fetal alcohol spectrum disorders (FASD) encompass the range of outcomes that may occur as a result of alcohol teratogenesis, including growth retardation, birth defects, facial dysmorphia, and central nervous system dysfunction. Exposure to alcohol during prenatal development disrupts midline expansion, sonic hedgehog signaling, and neural crest development, which makes the midline craniofacial and brain structures especially vulnerable (Sulik et al., 1984, 1986; Johnson et al., 1996; Smith et al., 2014).

The pituitary gland is a midline endocrine structure located along the base of the brain. Pituitary abnormalities have been noted in autopsy examinations of individuals with prenatal alcohol exposure (Coulter et al., 1993). Animal models support this effect and are dependent on the timing (gestational day: GD) of the prenatal alcohol exposure. Following exposure, the pituitary of fetal mice was absent (GD7: Godin et al., 2010), disproportionately enlarged (GD8: Parnell et al., 2009; GD10: O'Leary-Moore et al., 2010), or dysplastic (GD9: Kotch and Sulik, 1992). Alcohol's interference with the development of the pituitary gland could have lasting effects on endocrine function. An alteration of the hormonal milieu has been noted in infants and children with prenatal alcohol exposure. Higher basal cortisol levels were observed in 2-month old infants exposed to alcohol or cigarettes during gestation (Ramsay et al., 1996) and the amount of alcohol consumed during pregnancy was positively related to both the basal cortisol level and the post-stress cortisol response in 13-month old infants (Jacobson et al., 1999). School age children (6–14 years) with FASD displayed elevated salivary cortisol levels in the afternoon and bedtime as compared to controls (Keiver et al., 2015).

The effects of prenatal alcohol exposure on pituitary gland can be probed using magnetic resonance imaging (MRI). The volume of the pituitary gland, which fluctuates along with hormonal changes, has been postulated as an index of hormonal status in humans (MacMaster et al., 2006). During adolescence, coinciding with pubertal development, the structure of the pituitary gland changes in shape and increases in volume (Elster et al., 1990; Kato et al., 2002; MacMaster et al., 2007b) and there is a positive linear relationship between pituitary volume and levels of the gonadal hormones and sex steroids (Peper et al.,

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2010). Girls have a larger adolescent increase in pituitary volume than do boys (Elster et al., 1990; Kato et al., 2002; MacMaster et al., 2007b) and pituitary volume also surges during pregnancy (Dinç et al., 1998). Additionally, MRI measurements of the pituitary can provide insight into vasopressin levels stored in its posterior lobe. On T1-weighted MRI the neurohypophysis (i.e., posterior lobe of the pituitary) is hyperintense (i.e., a bright spot), but the signal intensity diminishes after water deprivation (Lee et al., 2001) or infusion of hypertonic saline into the blood stream (Teshima et al., 2008). The neurohypophyseal signal intensity change corresponds to blood plasma levels of vasopressin (Lee et al., 2001; Teshima et al., 2008). This suggests that T1-weighted MRI signal intensity of the neurohypophysis can be used to estimate vasopressin storage.

T1-weighted MRI was used to examine pituitary volume and signal intensity in male and female adolescents with and without histories of heavy prenatal alcohol exposure. We predicted that prenatal alcohol exposure would result in reduced pituitary volume and signal intensity.

2. Materials and methods

2.1. Subjects

Twenty-six adolescents with histories of heavy prenatal alcohol exposure (AE; 15 males, 11 females) and 27 controls (CON; 16 males, 11 females) completed magnetic resonance imaging as part of ongoing studies at the Center for Behavioral Teratology at San Diego State University. As part of these ongoing studies, Full Scale IQ scores (FSIQ, from the Wechsler Intelligence Scale for Children; Wechsler, 1991; Wechsler, 2004), socioeconomic status index scores (SES, measured by the Hollingshead Four Factor Index of Social Status; Hollingshead, 1975), and presence of psychopathology (defined as meeting criteria for any Axis I disorder based on caregiver report with the clinician assisted Computerized Diagnostic Interview Schedule for Children Version IV [DISC]; Shaffer et al., 2000) were available for all participants.

Study inclusion criteria required subjects to be age 13–18 years old and fluent English speakers. A confirmed history of heavy prenatal alcohol exposure was required for inclusion in the AE group. Exposure was established via the review of medical, adoption, or social service records or maternal self-report. If review of records indicated that the mother was alcohol abusing or dependent during pregnancy, this was considered evidence of heavy prenatal alcohol exposure. Direct maternal report was not available for 24 out of 26 of our subjects, as these children no longer resided with their biological mothers. However, maternal report was available for two children and for these cases heavy alcohol exposure (defined as average maternal consumption of 4 or more drinks per occasion at least once a week or an average of 14 drinks per week during pregnancy) was confirmed. In addition, children were examined by a pediatric dysmorphologist (KL Jones). A fetal alcohol syndrome (FAS) diagnosis was not required for inclusion in the AE group, but was indicated by 2 or more facial features and either growth restriction or microcephaly (Mattson et al., 2010). Nine adolescents in the AE group (35%) received an FAS diagnosis using these research criteria. For inclusion in the CON group, subjects must have minimal exposure to alcohol, defined as maternal consumption of no >1 alcoholic drink per week on average and never >2 drinks per occasion during pregnancy. Screening for prenatal alcohol exposure in the CON group was often determined through direct maternal report, as 25 out of 27 control subjects resided with their biological mothers.

Exclusion criteria for both groups included head trauma with loss of consciousness for >30 min, contraindication for MRI scanning (e.g., irremovable metal in the body or claustrophobia), or serious medical or psychiatric conditions that would prevent participation. The Institutional Review Boards of San Diego State University and the University of California, San Diego approved all study procedures. Parents or guardians signed a written informed consent/parental permission form and adolescent subjects signed an age-appropriate assent document. Subjects received a financial incentive for participation.

2.2. MRI data acquisition and processing

High-resolution T_1-weighted sagittal volumes were acquired for 53 subjects on a 3T GE Signa Excite scanner (General Electric, Milwaukee, WI) using an 8-channel head coil. To maximize our sample size, images from two separate MRI projects were combined. Images were acquired for 40 subjects with the following scan parameters: TR, 8 ms; TE, 3.1 ms; flip angle 8°; matrix 256 × 256 × 192; FOV, 256 × 256 mm; slice thickness 1 mm; acquisition time, 7 min and 24 s. For the remaining 13 subjects, images were acquired with parameters: TR, 8 ms; TE, 3.0 ms; flip angle 12°; matrix 256 × 256 × 192; FOV, 240 × 240 mm; slice thickness 1 mm; acquisition time, 7 min and 4 s.

Preprocessing on structural images was conducted using FreeSurfer v5.3 software (http://surfer.nmr.mgh.harvard.edu; Fischl et al., 2002). Estimated total intracranial volume (ICV) was calculated using FreeSurfer's automatic quantification, which included registration of the image to standard space. All data were visually inspected for quality control. FreeSurfer's automated processing was found adequate for most images; however, the skull-stripping step removed portions of the pituitary gland in 3 images (1 AE and 2 CON). These images were manually edited to restore the missing voxels and reprocessed.

2.3. Pituitary tracing

Fig. 1 displays a representative pituitary tracing. Using FreeSurfer's *tkmedit* tool, the pituitary gland was labeled. In the coronal view, the pituitary was identified and the gland was traced in all slices where it could be visualized. The infundibular stalk was not included in tracings. Labels were inspected and edited in the sagittal and horizontal planes ensuring that the final pituitary label conformed to the expected pituitary shape. A single analyst blinded to group assignment traced the pituitary. To assess intra-rater reliability a random sample of 10 images were selected and the pituitary was retraced. Pearson correlations demonstrated excellent intra-rater ($r = 0.93$, $p < 0.001$) reliability. Total pituitary volume was extracted for use in a between group analysis. We were also interested in examining signal intensity of the posterior pituitary, which is delineated from the anterior pituitary based on the signal intensity. However, upon visual inspection it was clear that there was substantial variation between subjects on this variable. We worried that a systematic bias would be introduced in delineating the borders of the posterior pituitary if the average signal intensity were different between AE and CON. Thus, we chose to trace the pituitary gland as a whole and extract the single voxel with the greatest signal intensity to determine if there may be group differences. Visual inspection revealed that the voxel used for the signal intensity analysis was located posterior to the infundibular stalk in all cases, providing an approximation of the posterior pituitary signal intensity.

2.4. Statistical analyses

Statistical analyses were conducted using SPSS 22. Results were considered significant at $p < 0.05$.

2.5. Subject characteristics

Differences in age, SES, and FSIQ were evaluated with separate 2 × 2 (exposure × sex) analysis of variance (ANOVA) analyses. Separate chi-squared analyses were conducted within group and sex to evaluate differences in race, ethnicity, handedness, and rate of psychopathology.