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Sex-related differences in auditory processing in adolescents with fetal alcohol spectrum disorder: A magnetoencephalographic study

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ABSTRACT

Children exposed to substantial amounts of alcohol in utero display a broad range of morphological and behavioral outcomes, which are collectively referred to as fetal alcohol spectrum disorders (FASDs). Common to all children on the spectrum are cognitive and behavioral problems that reflect central nervous system dysfunction. Little is known, however, about the potential effects of variables such as sex on alcohol-induced brain damage. The goal of the current research was to utilize magnetoencephalography (MEG) to examine the effect of sex on brain dynamics in adolescents and young adults with FASD during the performance of an auditory oddball task. The stimuli were short trains of 1 kHz "standard" tone bursts (80%) randomly interleaved with 1.5 kHz "target" tone bursts (10%) and "novel" digital sounds (10%). Participants made motor responses to the target tones. Results are reported for 44 individuals (18 males and 26 females) ages 12 through 22 years. Nine males and 13 females had a diagnosis of FASD and the remainder were typically-developing age- and sex-matched controls. The main finding was widespread sex-specific differential activation of the frontal, medial and temporal cortex in adolescents with FASD compared to typically developing controls. Significant differences in evoked-response and time–frequency measures of brain dynamics were observed for all stimulus types in the auditory cortex, inferior frontal sulcus and hippocampus. These results underscore the importance of considering the influence of sex when analyzing neurophysiological data in children with FASD.

1. Introduction

Exposure to moderate to heavy amounts of alcohol during pregnancy remains a leading preventable cause of intellectual disabilities in North America (Abel and Sokol, 1986; May and Gossage, 2001; Chudley et al., 2005; May et al., 2009). Children with fetal alcohol spectrum disorder (FASD) face a broad spectrum of cognitive and behavioral challenges, including deficits in sensory processing, attention, working memory and executive function (Mattson et al., 1998; Roussotte et al., 2010; Mattson et al., 2011; Riley et al., 2011). Although facial dysmorphia is characteristic of fetal alcohol syndrome (FAS), the severe end of the FASD spectrum, many children with FASD lack physical abnormalities and hence are often not diagnosed, even though sharing many of the same cognitive and behavioral issues (Mattson et al., 1998; Kodituwakku, 2009; Roussotte et al., 2010; Mattson et al., 2011). This latter group of children, labeled as showing alcohol related neurodevelopmental disorder (ARND), is known to display aberrant neural functions and subtle neuroanatomical differences in neuroimaging studies.

Delayed and/or abnormal brain development may contribute to deficits in cognitive function and increased behavioral issues in adolescents with FASD (Lebel et al., 2011; Triet et al., 2013). Brain regions particularly vulnerable to alcohol's teratogenicity include the frontal and parietal cortex, posterior sensory cortex, caudate, hippocampus, and cerebellum (for a review, see Roussotte et al., 2010). Although reduction in total brain volume is a common feature in FASD (Astley et al., 2009; Lebel et al., 2011), increased local cortical thickness has been reported in the parietal and frontal cortices (Sowell et al., 2002; Sowell et al., 2008) and in the inferior frontal, superior temporal, and middle temporal cortex (Yang et al., 2012). Yang et al., 2012 found that even children with ARND showed volume reductions in multiple brain regions, including the frontal, parietal, and temporal lobes,

Abbreviations: FASD, fetal alcohol spectrum disorder; FASDM, male participants with fetal alcohol spectrum disorder; FASDF, female participants with fetal alcohol spectrum disorder; HC, healthy control participants; HCM, male healthy control participants; HCF, female healthy control participants; RT, response time.

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although these volume reductions were due to reduced cortical surface area rather than thickness. Abnormal and delayed development of white matter tracts have also been seen in FASD in the posterior corpus callosum, anterior–posterior fiber bundles, superior longitudinal fasciculus and superior and inferior fronto-occipital fasciculus, and cerebellar peduncles (cf. Wozniak et al., 2011a,b; Spottiswoode et al., 2011; Triet et al., 2013; Green et al., 2013).

Adolescence is a period of marked change in brain organization. Functional neuroimaging studies reveal that typically developing adolescents exhibit weaker modulatory control from frontal areas compared to adults (Hwang et al., 2010). In a recent fMRI study of children from 7–14 years of age, FASD showed reduced activation bilaterally in the frontal, parietal and temporal cortex compared to controls, suggesting an impact of alcohol exposure *in utero* on maturation (Gautam et al., 2014). Increased frontal and parietal activation has been reported during the performance of spatial working memory task in ARND and go/no-go tasks in FASD (Malisza et al., 2012; Norman et al., 2013; O'Brien et al., 2013). Although differences observed in microvascular networks in a mouse model of FAS/partialFAS suggest some caution in the interpretation of these fMRI data (Jégou et al., 2012), electroencephalographic (EEG) and magnetoencephalographic (MEG) studies also support differences in measures of brain function in FASD. Deficits in auditory stimulus classification and inhibition have been reported in adolescents with FAS/partialFAS (Steinmann et al., 2011). Latency and amplitude differences of the P300 auditory event-related potential (ERP) in an oddball task discriminated between children with Down syndrome, FASD, and typically developing controls (Kaneko et al., 1996a). Auditory processing delays have also been observed in a MEG study of preschool children with FASD (Stephen et al., 2012).

The present study utilized MEG to investigate brain dynamics of adolescents with FASD during the performance of an auditory oddball task. This task probes development of a "top-down" perceptual expectation for a set of repeated (standard) tones, detection of "target" tones that elicit behavioral responses and processing of novel digital sounds in cortico-hippocampal circuits (Halgren et al., 1998). Sex-related differences in brain structure are known to emerge in typically developing adolescents, with increased volume of the amygdala in males and of the hippocampus in females (for a review, see Blakemore, 2012). Since prenatal ethanol exposure is known to produce sex-specific deficits in hippocampus in rodent models (Coleman et al., 2012; see also Helfer et al., 2012; Sickmann et al., 2014), we hypothesized that MEG measures of brain activation in the oddball data may reveal sex-specific differences for adolescents with FASD. Consideration of potential sexual dimorphism in neuroimaging and neurophysiological studies in adolescents with FASD is rare (although see Kaneko et al., 1996a).

The present effort will contribute novel information on sex-specific effects on brain function and motivate further attention to potential sexual dimorphism in studies of adolescents with FASD.

2. Methods

2.1. Participants

Forty eight adolescents and young adults in the age range 12–22 years were recruited for this study. High quality MEG data were obtained from 44 participants. One of these participants did not complete the MRI scan. For the participants utilized in the MEG analysis, twenty two of the participants (9 male, age 15.0 yrs, SD = 3.6 yrs; 13 female, age 15.5 yrs, SD = 2.8 yrs) were identified as FASD according to the modified Institute of Medicine criteria (Stratton et al., 1996). Of these, 9 were diagnosed with FAS (6 male and 3 female) and 13 with alcohol-related neurodevelopmental disorder (ARND) (3 male and 10 female). Twenty-two age- and sex-matched healthy individuals (HC; 9 male, M age 13.5 yrs, SD = 4.7 yrs; 13 female, M age 16.8 yrs, SD = 3.3 yrs) with no history of prenatal alcohol exposure, developmental delays, significant psychiatric or neurological problems served as controls. All of the participants were right handed (Edinburgh Handedness Inventory: Oldfield, 1971) and none of the participants had significant sensory problems (*e.g.* poor vision or hearing) or difficulty understanding the task demands.

Participants with FASD were recruited at the University of New Mexico Fetal Alcohol Diagnostic and Evaluation Clinic and healthy controls (HC) through flyers and word of mouth.

This study was approved by the University of New Mexico Health Sciences Center Institutional Review Board and was in full compliance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from the parents/legal guardians and/or participants dependent on the age and assent from minors in accord with the Institutional Review Board guideline of the University of New Mexico. Participants were compensated for their time and travel expenses.

Table 1
Comparison of FASD and HC on neuropsychological measures, response times to target stimuli and age.

Group comparisons:

Measure	FASD		HC		*d*	*t* (df)
	Mean	SD	Mean	SD		
IQ	81.78	10.05	100.47	9.93	1.87	5.53* (33)
Vocab	31.00	7.36	49.53	8.62	2.31	6.86* (33)
Matrix Reas	44.89	9.24	49.76	8.76	0.54	1.60 (33)
RT (ms)	579.58	157.99	514.86	94.06	−0.50	−1.54 (37)
Age (years)	17.30	2.66	17.37	2.61	0.03	0.08 (37)

Between group sex comparisons:

Measure	FASDM		HCM		*d*	*t* (df)
	Mean	SD	Mean	SD		
IQ	78.88	12.46	101.11	8.1	2.28	4.42* (15)
Vocab	29.50	7.09	50.0	7.05	3.08	5.97* (15)
Matrix Reas	41.88	11.34	48.78	10.85	0.66	1.28 (15)
RT (ms)	575.52	133.47	480.31	110.78	−0.82	−1.59 (15)
Age (years)	16.0	2.92	16.3	2.72	0.11	0.24 (18)
Measure	FASDF		HCF		*d*	*t* (df)
	Mean	SD	Mean	SD		
IQ	82.25	8.07	99.08	11.0	1.82	4.27* (22)
Vocab	31.55	7.63	48.42	9.95	1.98	4.53* (21)
Matrix Reas	46.45	7.06	50.58	5.4	0.69	1.58 (21)
RT (ms)	611.61	204.45	507.19	83.50	−0.69	−1.65 (23)
Age (years)	15.91	3.16	16.55	3.14	0.21	0.53 (25)

Within group sex comparisons:

Measure	HCM		HCF		*d*	*t* (df)
	Mean	SD	Mean	SD		
IQ	101.11	8.1	99.08	11.0	−0.213	−0.465 (19)
Vocab	50.0	7.05	48.42	9.95	−0.186	−0.406 (19)
Matrix Reas	48.78	10.85	50.58	5.4	0.230	0.502 (19)
RT (ms)	480.31	110.78	507.19	83.50	0.292	0.620 (18)
Age (years)	16.3	2.72	16.55	3.14	0.089	0.209 (22)
Measure	FASDM		FASDF		*d*	*t* (df)
	Mean	SD	Mean	SD		
IQ	78.88	12.46	82.25	8.07	−0.348	0.739 (18)
Vocab	29.50	7.09	31.55	7.63	0.288	0.594 (17)
Matrix Reas	41.88	11.34	46.45	7.06	0.527	1.086 (17)
RT (ms)	575.52	133.47	611.61	204.45	0.208	0.464 (20)
Age (years)	16.0	2.92	15.91	3.16	−0.028	−0.065 (21)

Note. FASD = fetal alcohol spectrum disorder. HC = healthy control. *d* = Cohen's d. RT = response time. IQ = full scale IQ from WASI. All effects computed as HC-FASD or male (M)–female (F).
* $p \leq .05$.