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Impaired Odor Identification in Children with Histories of Heavy Prenatal Alcohol Exposure

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Abstract

Prenatal alcohol exposure can lead to behavioral and cognitive impairments across multiple domains. Many of the brain regions impacted by prenatal alcohol exposure are also linked with olfactory processing, and odor identification deficits have been documented in certain neurological disorders associated with these brain regions. As odor identification following prenatal alcohol exposure is not well studied, we compared odor identification in children with prenatal exposure to alcohol (AE) to typically developing controls (CON) (N = 16/group). It was hypothesized that children in the AE group would perform more poorly than children in the CON group on the San Diego Odor Identification Test, an identification test of 8 common household odorants. Children exposed to alcohol during prenatal development were significantly impaired in olfactory identification (M = 5.95, SE = 0.37) compared to typically developing controls (M = 7.24, SE = 0.37). These findings confirmed the hypothesis that prenatal exposure to alcohol is associated with odor identification deficits, and suggest that further research is warranted to identify the mechanisms underlying these deficits, the integrity of brain areas that are involved, and to determine whether olfactory performance might contribute to better identification of children at risk for behavioral and cognitive deficits.

Keywords

Prenatal Alcohol Exposure; Fetal Alcohol Spectrum Disorders; Fetal Alcohol Syndrome; Odor Identification; Smell Impairment

Introduction

Recent research suggests that prevalence rates of Fetal Alcohol Syndrome (FAS) in the U.S. are at least 2 to 7 for every 1,000 in typical mixed race and socioeconomic populations, with this number growing as high as 2-5% of school-aged children when all diagnoses of Fetal Alcohol Spectrum Disorders (FASD) are considered (May et al., 2009). As one of the most

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prevalent preventable causes of birth defects and cognitive impairments in North America, the effects of prenatal exposure to alcohol have received a significant amount of attention in recent research (Mattson et al., 2011; Mattson & Riley, 2011; Sowell et al., 2008; Murthy et al., 2009).

While a diagnosis of FAS is based primarily on physical features, FASD incorporates a broader spectrum of alcohol-affected individuals; alcohol-exposed children with or without the physical markers show similar cognitive and behavioral deficits (Sampson et al., 1997; Mattson et al., 1998). Characteristic cognitive deficits include impairments in attention, IQ, executive functioning, verbal skills, arithmetic skills, visual-spatial functioning, and verbal and non-verbal learning (Chiodo et al., 2009; Kaemingk et al., 2003; Mattson et al., 2006; McGee et al., 2009; Streissguth et al., 1990; Streissguth et al., 1994; Vaurio et al., 2008). Behavioral problems associated with FASD include poor social and communication skills, adaptive abilities, hyperactivity, attention deficits, depression, and various conduct disorders (Crocker, et al., 2009; Streissguth et al., 1996). Overall, these children are more likely to be classified as disruptive, impulsive or delinquent and to suffer academic failure (Fast et al., 1999; Howell et al., 2006; Mattson et al., 2001).

In general, known neural effects of prenatal alcohol exposure in humans include overall reductions in brain volume, particularly within the frontal, temporal, and parietal cortices. Imaging studies have also shown the basal ganglia to be particularly reduced in size as well as both the hippocampus and the cerebellum, even when controlling for overall brain size (Mattson et al., 1996; Lebel et al., 2011). Overall increases in gray matter and decreases in white matter throughout the brain are also commonly seen, along with abnormalities of the corpus callosum. Specifically, prenatal exposure to alcohol results in the corpus callosum lying more anterior and inferior in posterior regions with relatively normal localization of anterior regions. Importantly, studies have linked the amount of corpus callosum displacement with deficits in verbal learning, as well as on other tasks requiring communication between the left and right hemispheres (Korkman et al., 1998; Sowell et al., 2001). Within the frontal region, the cortex has been shown to be thicker for those exposed to alcohol than for controls, while extent of brain surface was smaller in the anterior and orbitofrontal areas (Sowell et al., 2001; Lebel et al., 2011).

Animal studies have also found neurological and behavioral changes resulting from prenatal exposure to alcohol, particularly in the domain of olfactory functioning. In rodents, exposure to ethanol in utero resulted in a “tuning” of the olfactory epithelium to ethanol, leading infantile rats to develop a specific behavioral response to ethanol and to also become less responsive to other odorants (Youngentob et al., 2007). This “tuned” behavioral response to ethanol is characterized by an unconditioned sniffing and neurophysiological response to ethanol odor in infantile and adolescent rats, and is linked to the increased ethanol avidity during adolescence (Barron & Riley, 1992; Middleton et al., 2009).

Odor identification is a task that requires not only detection of an odor, but the ability to name it, implying memory for previous experience with the odor. Quantitative measurement of the ability to identify odors may be beneficial in helping to identify individuals with histories of prenatal alcohol exposure. Importantly, many of the brain regions required for successful odor identification, such as the orbitofrontal cortex, anterior and medial temporal lobe areas, and limbic system, are all known to be affected by prenatal exposure to alcohol, even when the full criteria for FAS are not met (Jones-Gotman et al., 1997; Larsson et al., 1999; Mattson et al., 2001; Mattson, et al., 2010). Moreover, functional imaging studies have reported that those with an FASD show abnormal patterns of neural activation during tasks of verbal working memory, verbal learning, and sustained attention, which are also important to successful odor identification (Lebel et al., 2010). Tests of odor identification

have exhibited significant ability to identify other neurological disorders also known to affect orbitofrontal cortex, anterior and medial temporal lobe areas, and the limbic system, such as Alzheimer's disease (Murphy et al., 1998; Murphy, 2002; Murphy et al., 2003; Calhoun-Haney & Murphy, 2005; Wilson et al., 2011).

However, to the best of our knowledge, there are no published studies that investigated the relationship between prenatal exposure to alcohol and odor identification abilities. Thus, the aim of the current study was to investigate the effects of prenatal exposure to alcohol on odor identification performance. It was hypothesized that those with confirmed histories of prenatal exposure to alcohol would perform significantly worse than normal controls on the San Diego Odor Identification Test.

Materials and Methods

Subjects

Subjects were 16 children and adolescents with heavy prenatal alcohol exposure (AE) and a control group of 16 typically developing peers with no prenatal exposure to alcohol (CON). Both the AE and CON groups ranged from 6 to 16 years in age. The two groups were matched on age, sex, and race/ethnicity (Table 1). All subjects were recruited as part of a larger ongoing study of the behavioral teratogenicity of alcohol. Alcohol-exposed children were recruited via professional referral or caregiver self-referral, while children in the control group were recruited from the community through advertising at child-related agencies and venues.

To be included in the current study, children were required to be at least 5 years old or have entered kindergarten prior to administration of the odor identification test. Inclusion in the AE group required a history of heavy prenatal alcohol exposure, which was defined as at least 4 drinks per occasion at least once per week or 14 drinks per week during pregnancy. Prenatal alcohol exposure was determined through multisource collateral report, including review of available medical, social service, and adoption agency records or maternal report, when available. Subjects in the AE group were also evaluated by a dysmorphologist with expertise in teratogenesis (Kenneth Lyons Jones, MD). None of the children included in this study met the criteria for FAS diagnosis.

Subjects were excluded if they had a history of significant head injury or loss of consciousness greater than 30 minutes, evidence of other known causes of mental deficiency, were non-fluent in English, were adopted from abroad after age 5 or less than 2 years before assessment, or had current allergies or upper respiratory infection, or had a psychiatric or physical disability that would prevent study completion.

Procedure

All procedures were conducted in accordance with the ethical standards of the San Diego State University Review Board and with the Helsinki Declaration of 1975, as revised in 1983. Written parental consent and subject assent was obtained for each subject prior to testing, and all test administrators were blind to group status of the subject. Testing was completed at the Center for Behavioral Teratology (CBT), San Diego State University.

Odor Identification Test

The San Diego Odor Identification Test (SDOIT; Murphy et al., 1994; Murphy et al., 2002) is an 8-item test consisting of common odors typically found in the home (e.g., chocolate, peanut butter). The task is ideal for children because of the simple nature of the instructions, and it requires no reading ability. Previous research demonstrates high (0.86) test-retest

reliability in children (Murphy et al., 1994), and it has been used successfully with other samples of children, e.g., those with Down Syndrome (Sliger et al., 2004). Odorants were presented to the subject in opaque plastic jars to prevent visual clues that might influence odor identification responses. Prior to administration, subjects were presented with a picture-based cue sheet depicting 20 pictures: 8 of the pictures were of the target odor items and twelve were distracters. The cue sheet was used as a non-lexical identification response aid, and to prevent any response bias related to naming problems. All subjects were asked to identify all the pictures on the cue sheet prior to testing, and all were able to do so. They were then presented each of the eight target odors in random order. The subject was asked to close his/her eyes, the odor jar was held beneath the subject's nose for 5 seconds and the subject was instructed to smell. The subject was allowed to respond verbally or by pointing to the picture they perceived as identifying the odor. An interstimulus interval of 45 seconds was used to avoid adaptation. Performance was evaluated using raw scores by summing the number of correct target odors identified, with a possible score ranging from 0 to 8.

Statistical Analyses

We initially examined the data to ensure compliance with the assumptions of analysis of covariance and to evaluate descriptive characteristics of the variables. Group differences on odor identification performance were analyzed with Analysis of variance (ANOVA). Alpha level was set at $p < 0.05$. Analysis was conducted using SPSS version 18.0.

Results

Table 1 lists demographics and group means on the SDOIT. Groups were well matched on age, sex, and race/ethnicity.

As shown in Figure 1, results of the ANOVA revealed that subjects in the AE group performed significantly poorer than those in the CON group on the odor identification task, $F(1, 30) = 4.81$, $p < 0.05$, Cohen's $d = 0.77$. The mean number of odors identified for the AE group was 5.95 (*S.E.M.* = 0.37) odors, while for the CON group it was 7.24 (*S.E.M.* = 0.37) odors.

Discussion

The aim of the current study was to investigate odor identification performance in children and adolescents with prenatal alcohol exposure. The findings confirmed the hypothesis that children and adolescents who were exposed to alcohol prenatally would perform worse on the San Diego Odor Identification test than typically developing peers who were not exposed to alcohol during prenatal development.

These results are consistent with the finding that many children who do not manifest the physical features necessary to meet diagnostic criteria for FAS nevertheless sustain underlying central nervous system deficits that result in cognitive and behavioral abnormalities (Maier et al., 1999; Sampson et al., 1997; Mattson et al., 1998).

To our knowledge this is the first study to report the results of direct testing of odor identification in children exposed to alcohol during prenatal development. Caregivers of children with FASD have suggested the potential for general sensory processing deficits (Franklin et al., 2008), including tactile, taste, and smell sensitivity, problems with auditory filtering, visual and auditory sensitivity, and either an under-responsiveness to or excessive seeking of sensation. Studies that relied on caregiver reports and questionnaires have noted the limitations that such measures may be biased depending on which caregiver completes the report (Franklin et al., 2008) and may not reflect the child's internal experience. The use

of a quantitative psychophysical measure of odor identification in children with FASD addresses these limitations by testing the child directly on a standard measure of olfactory processing. Furthermore, the nature of the response measure reduces the confounding effects of verbal limitations, and allows for the inclusion of younger subjects.

Effects on fetal development may be dependent upon the timing and/or duration of alcohol exposure during pregnancy. For example, Maier et al. (1999) found decreased volume in the olfactory bulb of rats exposed to alcohol during a time point equivalent to the third trimester in humans, but not during the first or second trimesters. However, overall volume of the olfactory bulb was reduced in those exposed across all trimesters compared to those exposed during the first or second trimester only. Similarly, regional brain volume decreases correlating with level of prenatal alcohol exposure have been found in multiple brain regions in humans (Roussotte et al., 2012; Lebel et al., 2011). It is speculated that olfactory deficits seen in the present study could be due to cellular or volume changes in brain structures involved in olfactory processing or decreased connectivity between sensory processing regions. Investigation of the effects of timing and duration of exposure are important areas for future study.

There are some limitations to this study. It is important to note that further studies are needed to determine the relative contributions of olfactory system integrity and impairment in cognitive domains such as attention or memory to the performance deficits seen in this study. Utilizing a battery of measures that includes an olfactory threshold test will contribute to elucidation of the nature of olfactory functional impairments. It should also be noted that reports of maternal alcohol consumption were obtained retrospectively, which could have biased responses. Despite these limitations, the current study sets a precedent and points to the need for future explorations into olfactory function and psychophysical testing in children and adolescents prenatally exposed to alcohol.

In summary, the current study supports the hypothesis that olfactory identification is impaired in children with prenatal alcohol exposure compared to non-exposed typically developing peers. The results suggest that further research is warranted to identify the mechanisms underlying these impairments, the integrity of brain areas that are involved, and to determine whether olfactory performance might contribute to better identification of children at risk for behavioral and cognitive deficits. Developing a comprehensive description of the impact of fetal alcohol exposure on olfactory function will contribute to the neurobehavioral profile of FASD, which may improve clinical identification and intervention for this group of children.

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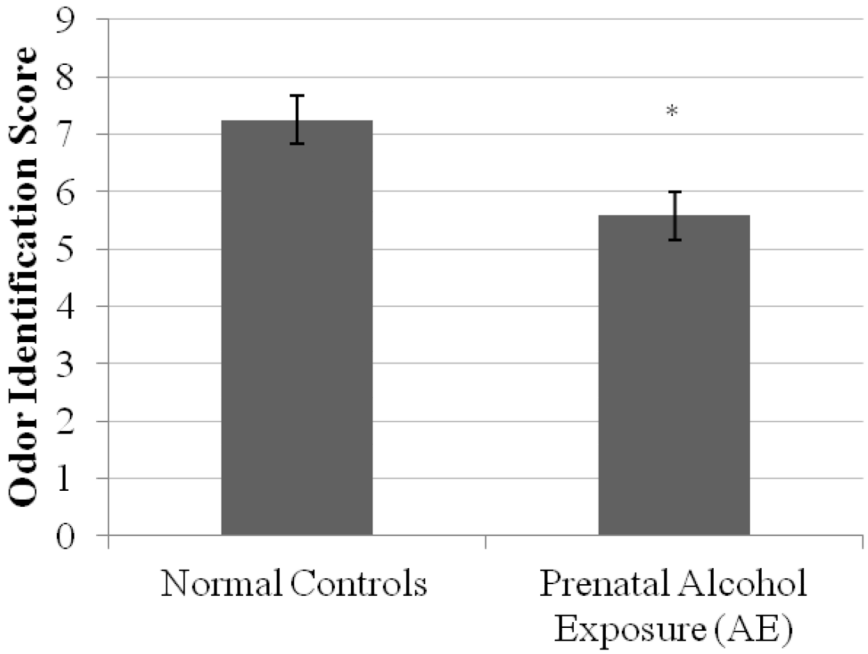

Figure 1.
Mean +/- S.E.M. odor identification scores by group.

Table 1
Participant Demographics and Performance

Gender, M/F
Age, Mean (SE)
Race
Caucasian
African American
White/Asian
Ethnicity
Hispanic
Non-Hispanic
SDOIT, Mean (SE)

Note. SDOIT = San Diego Odor Identification Test.