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Prenatal Alcohol Exposure Selectively Enhances Young Adult Perceived Pleasantness of Alcohol Odors

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Abstract

Prenatal Alcohol Exposure (PAE) can lead to life-long neurobehavioral and social problems that can include a greater likelihood of early use and/or abuse of alcohol compared to older teens and young adults without PAE. Basic research in animals demonstrates that PAE influences later postnatal responses to chemosensory cues (i.e., odor & taste) associated with alcohol. We hypothesized that PAE would be related to poorer abilities to identify odors of alcohol-containing beverages, and would alter perceived alcohol odor intensity and pleasantness. To address this hypothesis we examined responses to alcohol and other odors in a small sample of young adults with detailed prenatal histories of exposure to alcohol and other drugs. The key finding from our controlled analyses is that higher levels of PAE were related to higher relative ratings of pleasantness for alcohol odors. As far as we are aware, this is the first published study to report the influence of PAE on responses to alcohol beverage odors in young adults. These findings are consistent with the hypothesis that positive associations (i.e., “pleasantness”) to the chemosensory properties of alcohol (i.e., odor) are acquired prenatally and are retained for many years despite

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare regarding this work.

Preliminary reports of some of these findings were presented to the annual meeting of the Research Society on Alcoholism in San Francisco in 2012 (cf, Chiodo, et al., 2012), and at the Festschrift Symposium honoring Dr. Norman E. (“Skip”) Spear in Binghamton, NY, May, 2014.

myriad interceding postnatal experiences. Alternate hypotheses may also be supported by the results. There are potential implications of altered alcohol odor responses for understanding individual differences in initiation of drinking, and alcohol seeking and high-risk alcohol-related behaviors in young adults.

INTRODUCTION

Prenatal alcohol exposure (PAE) can lead to life-long neurobehavioral, cognitive and social problems that comprise the Fetal Alcohol Spectrum Disorders (FASD; Mattson, et al, 2011). Behavioral expressions of FASD include a greater likelihood of early use and/or abuse of alcohol and other substances compared to non-exposed adolescents and young adults. Early alcohol/substance use has been characterized as a “secondary disability” associated with Fetal Alcohol Syndrome (FAS) in teens (Streissguth et al., 1996). PAE was related to early initiation of alcohol use as well as to drinking-related problems at 14 and 21 years of age (Baer et al., 1998; 2003; Streissguth et al., 2007). These results were independent of maternal demographics, smoking or drug use during pregnancy, and familial postpartum alcohol problems.

Several factors may explain the origins of this increased risk for early alcohol use/abuse after PAE. These factors include teratogenic influences of alcohol on physiological and/or neural processes relevant to alcohol metabolism, sensitivity or reward properties (Abel & Hannigan, 1995), as well as postnatal parental drinking and/or smoking during a person’s childhood or adolescence (Sher et al., 2005). In addition, it has been argued on the basis of an association between PAE and subsequent alcohol use disorders and/or dependence that an additional factor is some non-teratogenic “biological origin of adult alcohol disorders” (Alati, et al, 2006; 2008), although the nature of this factor has not been identified.

Extensive basic research in animal models demonstrates that prenatal or early neonatal alcohol exposure alters a variety of later behavioral (Abate, et al., 2008; Becker et al., 1993; 1993; Chotro & Arias, 2006; Middleton et al., 2009; March et al., 2009), consummatory (Chotro et al., 2007; Díaz-Cenzano et al., 2014; Miranda-Morales et al., 2014; Shea et al, 2012; Youngentob & Glendinning, 2009), pharmacological (Díaz-Cenzano et al., 2014; Pautassi et al., 2012), biochemical (Middleton et al., 2009), and physiological (Eade et al, 2010; Taylor et al., 1981; Weinberg et al., 1995) responses to alcohol. Possible means by which PAE influences postnatal responses to and ingestion of alcohol include altered chemosensory experiences of alcohol and/or learning about the rewarding (or aversive) properties of alcohol cues *in utero* (e.g., Arias & Chotro, 2005; Chotro & Arias, 2006; Chotro et al., 1991; 2009; March et al., 2009; Pautassi et al., 2012; Youngentob & Glendinning, 2009); ideas articulated well in the theoretical review by N. Spear and Molina (2005). PAE leads reliably to altered biobehavioral responses to sensory cues associated with alcohol (Dominguez et al., 1998; N. Spear & Molina, 2005), including altered learned responses to paired alcohol odors and tastes after brief PAE (Abate et al., 2000; Arias & Chotro, 2005; Chotro, et al., 1991; Pautassi et al., 2012). In rats, even low-dose alcohol exposure during fetal development is associated with later increases in alcohol ingestion

(Abate et al., 2008; Chotro & Arias, 2006; Chotro & Molina, 1990; Youngentob & Glendinning, 2009).

While animal studies have shown that PAE alters various responses to alcohol odors (Chotro & Arias, 2006; N. Spear & Molina, 2005), PAE also impairs olfactory function for other odors. For example, PAE mice had more difficulty than non-exposed mice in discriminating similar odors (spearmint *versus* caraway) in a task that controlled for differences in learning and memory (Akers et al., 2011). Akers et al., also reported that largest reductions in brain area size by high-resolution MRI in these mice was found in the olfactory bulb. Although Barron and Riley (1992) also reported that PAE was associated with decreased volume of the olfactory bulb in rats, they found no evidence that PAE impaired the ability of pre-weanling rats to detect a novel odor measured by a change in respiration.

There is evidence suggesting that human infants of mothers who drank alcohol during pregnancy also appear to respond to or recognize alcohol odors differently than infants of mothers who abstained while pregnant. Of the few studies that examined how PAE may affect alcohol preference and alcohol-seeking behavior in infants, teens or adults (Alati et al., 2006, 2008; Baer et al., 1998, 2003; Faas 2000; Yates et al., 1998), some included covariate controls (e.g., Baer 1998, 2003). Each study reported increased alcohol-associated problems related to PAE; none addressed specific olfactory or gustatory responses to alcohol. A study of 5- to 10-year-old children reported that 15 of 44 children with some kind of “FASD” had a “definite difference” in “taste/smell sensitivity,” but there was no comparison group (Franklin et al., 2008). One prior report using the San Diego Smell Identification Test suggested that PAE altered olfactory sensitivity in children (Bower et al., 2013). We are aware of no published studies assessing differences in hedonic responses to, or ratings of pleasantness of alcohol odors by people who had been exposed prenatally to alcohol compared to those who were not alcohol exposed.

We hypothesized that increasing levels of PAE would alter responses to alcohol odors in young adult men and women. Consistent with prior human studies, we hypothesized that increasing levels of PAE would alter responses to alcohol odors and be related to poorer abilities of young adults to identify and rate odors, especially the odors of alcohol-containing beverages. Specifically, we hypothesized that PAE would be associated significantly with: 1) impaired recognition of odors; and altered ratings of perceived alcohol odor 2) intensity and 3) pleasantness. We examined simple responses to chemosensory properties (odor) of alcohol (ethanol) and other odorants in a small sample of young adults from a large established prospective longitudinal cohort with detailed prenatal and current histories of experiences with alcohol and other drugs. We also considered other select prenatal and current environmental factors thought to mediate or moderate relations among PAE and ratings of alcohol pleasantness, including proximity to other individuals who drink, especially current caregivers.

METHODS

The Wayne State University IRB approved all study procedures and signed informed consent was obtained from all participants prior to interviews and testing.

Participants

Participants (n=75) were selected from our large, previously established prospective cohort of 18- to 19-year-old male and female urban African-Americans from the longitudinal “SCHOO-BE” study described previously in detail (e.g., Delaney-Black et al., 2004; 2010). Recruitment for this study began with the oldest teen who participated in the age 18- to 19-year follow-up assessment and moved forward until a sample of 75 was obtained for this report. The SCHOO-BE sample was identified initially from a pregnancy sample recruited in 1988–1991 of the biologic mothers of current study participants (cf., Delaney-Black et al., 2004; 2010). Exclusions in the original pregnancy study included known HIV-positive mothers, repeated pregnancies from the same mother, or major congenital malformations of the offspring identified at birth.

All female young adult participants were pre-screened for their current pregnancy status during a pre-enrollment telephone recruitment call. Those who indicated that they were pregnant were asked to delay participation until after giving birth. Female participants who were eligible for testing were asked to submit to an hCG urine pregnancy test prior to participation since the long-term effects of the selected odors on a fetus are unknown. Upon arrival to the lab for testing, two female participants tested pregnant and thus did not complete the odor assessment; they did complete the interview.

Prenatal Alcohol Assessment

In the original prospective cohort, women in the antenatal clinic reporting peri-conceptional alcohol consumption averaging at least 1.0 ounce of absolute alcohol per day (AAD) – the equivalent of about two standard drinks per day – were recruited. A random sample of approximately 8% of lower level drinkers and abstainers were also invited to participate. In addition, all pregnant women reporting any cocaine use were recruited. At every antenatal clinic visit, semi-structured timeline follow-back interviews (Sokol, et al., 1985) solicited information about each mother’s alcohol consumption and drug use for the previous two weeks. Mothers were asked to recall what they drank, both at the time of the first visit, which on average occurred at the 23rd week of gestation (range: 6 to 38 weeks), and their drinking around the time of conception. Most women (90.2%) were not interviewed until after the first trimester. Detailed information regarding beverage type, specific drinking habits, binge drinking, alcohol consumption (as number of standard drinks) at particular times of the day and days of the week was obtained. Drinking volume was noted for each day. Based on self-reported drinking, we calculated several alcohol consumption measures: average ounces of absolute alcohol *per day* at: 1) conception (AAD0), 2) at the first prenatal visit (AAD1) and 3) across pregnancy (AADXP); as well as average ounces of absolute alcohol *per drinking day* at 4) conception (AADD0), 5) at the first prenatal visit (AADD1), and 6) across pregnancy (AADDXP). We, and others, have effectively used these measures of alcohol use to examine prenatal alcohol-related outcomes (e.g., Beblo et al., 2005; Burden et al., 2005; Jacobson et al., 1994; 1998; 2002; Nordstrom-Bailey et al., 2004). In addition, at the first antenatal visit we assessed problems associated with drinking with the 25-item Michigan Alcoholism Screening Test (MAST; Selzer, 1971), the CAGE screen (Ewing, 1984), and the 4-item T-ACE (or TACER-3) screen (Sokol et al., 1989; Chiodo et al, 2010).

The T-ACE/TACER-3 screen includes a question about “tolerance” – the “T” in “T-ACE/TACER-3” – asking how many drinks it takes to feel high.

At-Risk Alcohol Metric

From all these individual alcohol assessment measures and instruments, a metric of prenatal “At-Risk Alcohol Exposure” (ARAE) was calculated (cf, Chiodo et al., 2009). The ARAE metric dichotomized participants into those “at risk” or not. The ARAE metric defined a person “at risk” if any of one of the component prenatal drinking measures met the following criteria (see Chiodo et al., 2009): AAD0 1.0 oz.; AAD1 0.5 oz.; AADXP 0.5 oz.; AADD0 2.5 oz.; AADD1 2.5 oz.; AADDXP 2.5 oz.; MAST 5; CAGE 2; T-ACE 3 (i.e., the TACER-3 cut-point; Chiodo et al., 2010). With the exception of the T-ACE, all cut-points are based on standard definitions of “at-risk drinking” (cf. American College of Obstetrics & Gynecology, 2006; Jacobson and Jacobson, 1994; Russell et al., 1994). The American College of Obstetrics & Gynecology (2006) currently recommends a cut-point of 2 for the total T-ACE score which maximizes sensitivity in identifying women drinking at any level (Sokol et al., 2003). We had demonstrated previously that a total score cut-point of 3 or more rather than 2 or more on the T-ACE (i.e., the “TACER-3” screen), improved prediction of which pregnant women were consuming higher levels of alcohol, reduced “false positives” in detecting at-risk drinking, and improved prediction of alcohol-related neurobehavioral outcomes in children (Chiodo et al., 2009; 2010; 2014).

Caregiver Alcohol Use

At the age 14-year visit, caregivers were also queried about their own current alcohol consumption. For all women reporting any drinking, information about the type and pattern of drinking on each day during a typical week was also obtained. Measures of average amount of absolute alcohol consumed during a week (AAD) and average amount of absolute alcohol per drinking day (AADD) were also constructed.

Young Adult Risk Alcohol Use

To assess the young adults’ own current risk alcohol use, participants also completed the TACER-3 screen. The TACER-3 is the modification of the original T-ACE noted above using a total score cut-point of 3 which increases specificity while maintaining sensitivity equivalent to the original report (Sokol et al., 1989) for identifying risk drinking.

Control Variables

At the age 14-year visit, the primary caregiver, usually the biological mother (96%), was interviewed on many control variables for use in statistical analyses. These included assessments of the home environment, parenting quality, maternal age at the time of the first prenatal visit, primary caregiver SES, IQ, and education, and prenatal exposure to cigarettes, marijuana, and cocaine. A modified Home Observation for Measurement of the Environment (the “HOME”; Caldwell & Bradley, 1984) was used to evaluate parenting quality and home environment. Socio-economic status (SES) was estimated using Hollingshead’s 4-factor index (Hollingshead, 1975). For a detailed discussion, see Delaney-Black et al, 2011.

Odor Function Testing

Prior to testing, all participants rinsed their mouth with water and were told to refrain from chewing gum or mints, eating or drinking, and smoking or using chewing tobacco until testing was completed. A research assistant conducted confidential participant interviews about demographic characteristics and past and current alcohol and drug use.

Smell Identification Test—To assess basic olfactory function, all young adults completed the University of Pennsylvania Smell Identification Test (UP-SIT, Doty et al., 1984; 1989). The UP-SIT is a 40-item self-administered “scratch-and-sniff”-type test with high test-retest reliability ($r=0.94$; Doty et al., 1989) and the ability to predict a variety of developmental or progressive neural disorders and psychopathologies (e.g., Doty, 1991; Doty et al., 1995, McKeown et al., 1996; Wang et al., 2010). Performance on the UP-SIT reveals olfactory dysfunction as anosmia or mild, moderate, or severe smell loss (Doty et al., 1984). UP-SIT results are sex-influenced, so males and females are considered separately.

Alcohol Odors Assessment via the “Bottle Test”—The alcohol odor assessment was based on work by Schmidt and Beauchamp (1988) and Mennella and Garcia (2000). Odor stimuli were prepared and presented via 140-ml plastic (HDPE) squeeze bottles with flip-up caps. Each odorant solution (3 ml per bottle) was prepared in isolation and in a manner preventing cross-contamination of odors. See Table 1.

The translucent squeeze bottles were covered in foil and kept out of sight at least 2 feet from the participants. Odor presentation order was random. One at a time, the top of each opened bottle was positioned 3 cm from the participants’ nose. For each odor, “puffs” were delivered from the squeeze bottle to each nostril. Each young adult was given three attempts to identify the odor, if needed, with a 30-sec interval between each puff. The literal response was recorded and later coded as ‘correct’ or ‘incorrect’. Participants also rated, on a 5-point Likert scale, the pleasantness of the odor (1=Very Unpleasant; 2=Unpleasant; 3=Neutral; 4=Pleasant; 5=Very Pleasant), and odor intensity (1=No odor, 2=Faint odor ; 3=Moderate odor; 4=Strong odor; 5=Extremely Strong odor). A visible scale was available to aid participant ratings.

Statistical Analyses

Prior to analyses, checks were performed for missing and out-of range data and for deviations from normality. To evaluate the relations between PAE and odor variables, hierarchical regressions were utilized entering PAE and 14-year caregiver alcohol use in the first step and then all covariates simultaneously in the second step using forward entry ($p<0.05$ to enter, $p<0.10$ to remove). Subsequent direct comparisons and other follow up analyses were used to elaborate the nature of the impact of PAE.

RESULTS

Participants

The mean participant age was 20.9 years ($SD = 0.5$, range = 19.0 to 21.7). There were more females (61.3%) than males (males = 38.7%; $\chi^2 = 3.85$, $p = 0.05$). We found that 9.3% of

young adult participants were positive on the TACER-3 screen administered (“Young Adult” TACER-3 in Table 2). Among the participants who reported any drinking, the mean number of drinks they needed to feel “high” was just over three (i.e., 1.7 oz. of absolute alcohol); and 57.3% of them said they needed two or more drinks (see Table 2).

The mean age of the biologic mothers of the participants was 26.4 years old at their first prenatal visit. Among these women, 42.7% had used cocaine during the pregnancy and just over 25% reported regular cocaine use. Cocaine, marijuana and cigarette use were controlled for statistically in all regression analyses. Maternal in-pregnancy alcohol use and caregiver alcohol use at the participant’s 14-year assessment are also shown in Table 2. Based on the “ARAE” alcohol risk metric, ~ 30% of the mothers in this sample reported risk alcohol use during pregnancy; the TACER-3 screen identified 22% at risk for pregnancy alcohol use.

Olfactory Function (UP-SIT Test)

Consistent with population characteristics of olfactory performance on the UP-SIT (Doty et al., 1995), there was a significant difference between males and females in identifying odors ($t = -3.09$, $df = 58$, $p = 0.003$). The mean UP-SIT scores for males was 31.9 ($SD = 4.5$) and for females was 34.8 ($SD = 2.8$). Among males, 30% scored below the task-defined “cut-off” score of 31 indicating olfactory dysfunction, while 20% of females scored below their “cut-off” score of 33 indicating olfactory dysfunction. Participants with higher risk PAE as indicated by the ARAE metric identified significantly fewer odors on the UP-SIT. The UP-SIT score was included in regressions evaluating the influence of PAE.

Odor Identification, Intensity, and Pleasantness (The “Bottle Test”)

Descriptive statistics for participant report of odor identification and ratings of intensity and pleasantness in the “bottle test” are in Table 3. The odors of mint and 200-proof alcohol, as well as the lack of an odor for water, were most often identified correctly (89%, 73%, & 77%, respectively). In contrast, the odors of gin, flowers, and spoiled milk were identified correctly least often (11%, 13%, & 20%, respectively). The rating of water as the least intense and of 200-proof alcohol as the most intense was interpreted as evidence of test validity. Overall, all the odors other than water were rated as intense.

Generally, the alcohol-related odors were rated as less pleasant (range of means = 1.96 to 2.79) than the non-alcohol odors (range of means = 3.03 for water to 3.88 for bubble gum), with the exception of “spoiled milk” which was rated most unpleasant (rating = 1.86). Since the most frequent response for water pleasantness was “there is no odor,” no value was entered for these 42 participants (56% of the sample). Among the other participants, 21 (28% of the sample) rated water pleasantness as “neutral.” Since only 14 non-neutral responses were made (18.6% of the sample), the effects of PAE on ratings of water pleasantness were not analyzed further.

Relations between Prenatal Alcohol Exposure and Odor Responses

Identification and Intensity—The only effect of PAE on ratings of odor *identity* in the “Bottle Test” was a significantly lower identification of “bubble gum” odor, as a function of an increasing maternal TACER-3 score ($p < 0.05$; Table 4). There was also a significant

positive relation ($p < 0.05$) between being Maternal TACER-3-positive (when controlling for young adult tolerance) and incorrectly identifying the 200-proof alcohol odor (Table 4). There was no effect of PAE (Maternal ARAE or TACER-3) on ratings of odor *intensity* in the “Bottle Test” (Table 4).

Pleasantness—There were significant positive relations between PAE for both the ARAE metric and TACER-3 score and ratings of pleasantness for the odor of gin ($p < 0.05$) and mean alcohol odors overall ($p < 0.01$). The higher the maternal prenatal alcohol risk, the relatively higher were the young adult participants’ ratings of alcohol odor pleasantness (Table 4). This relation was seen even when controlling for young adult alcohol tolerance suggesting the result is not influenced by more frequent alcohol use. There was also a marginally significant positive relation between the ARAE metric and the pleasantness rating of the spoiled milk odor ($p < 0.10$; Table 4). Participants whose mothers were positive for at-risk alcohol use during pregnancy (ARAE-positive) reported spoiled milk as more pleasant (or less unpleasant) than ARAE-negative young adults not exposed to at risk alcohol during pregnancy ($p < 0.10$) (Table 4). Further, direct comparisons of the mean pleasantness ratings of alcohol by young adults relative to their ARAE scores (Table 5) also reveals significant relatively higher ratings of pleasantness of the odors of gin and mean alcohol overall ($p < 0.05$) for the “At-Risk” PAE (e.g., ARAE-positive) participants. Marginally significant higher ratings of pleasantness of whiskey ($p < 0.10$) for the “At-Risk” PAE (e.g., ARAE-positive) participants were also found.

DISCUSSION

The key finding from our controlled analyses is that higher levels of prenatal alcohol exposure (PAE) are related to higher relative ratings of pleasantness for alcohol odors in this small sample of young adults from our prospective longitudinal cohort. As far as we are aware, other than our own earlier abstract (Chiodo et al, 2012), this is the first published study to assess the influence of PAE on older teen/young adult responses to the odors of alcohol and alcohol beverages. The one previous study reporting differences in olfactory function after PAE at 11- to 12-years of age did not test alcohol odors (Bower et al., 2013). Our findings for alcohol odors are consistent with the hypothesis that positive associations to the chemosensory properties of alcohol are acquired prenatally (Chotro & Arias, 2006; Spear & Molina, 2005). It is remarkable that the relatively greater alcohol odor pleasantness ratings associated with PAE were found many years later, after myriad interceding postnatal experiences. It is important to acknowledge that life-long post-natal and current experiential factors may have more proximal influences on ratings of alcohol odors, but this does not diminish the relation to PAE demonstrated here. The implications of altered alcohol odor responses for understanding the initiation of drinking and differences among teens in alcohol preference, alcohol-seeking, and high-risk alcohol-related behaviors, all remain to be examined.

The PAE-associated relative differences in alcohol odor pleasantness ratings we found occurred in the absence of either significant differences in the ability to identify alcohol odors, or in the ratings of alcohol odor intensity. Thus the general olfactory dysfunction in these older teens/young adults with PAE suggested by differences in the UP-SIT test results

is not the source of PAE influences on pleasantness ratings of alcohol odors. It is important to note also, that the mean differences in alcohol odor pleasantness ratings between young adults with and without PAE were relative differences. Differences in alcohol odor ratings after PAE are as validly considered to indicate “less unpleasant” as “more pleasant” ratings. The mean alcohol odor pleasantness ratings for the young adults with PAE were still below or near “neutral” (range = 2.14 to 3.18), although higher than in those without PAE (range = 1.89 to 2.74). Yet the effect of PAE is not only to reduce ratings of unpleasantness, since 31.8% of PAE participants, based on Maternal TACER-3 scores, rated the odor of gin as “pleasant” or “very pleasant” compared to only 13.7% of teens without at-risk PAE. Also, young adults with PAE were more than twice as likely to rate mean alcohol odors overall as “pleasant” compared to those without PAE (13.6% versus 5.6%).

The finding that PAE was associated with compromised general olfactory function in young adults in the UP-SIT test with 40 non-alcohol odors is consistent with the results of a prior study of 22 younger boys and girls (11 to 12 years old) reporting that PAE was associated with poorer performance on the 8-item San Diego Odor Identification Test (Bower et al., 2013). It is important to recognize that the generally specific ratings of relatively greater alcohol odor pleasantness in the older participants with PAE in the present study occurred even in the presence of this apparent olfactory dysfunction. The UP-SIT focuses on odor identification but poor performance on the UP-SIT has been shown to indicate a broader olfactory dysfunction. It is also possible that PAE may be associated with a reduction in the relative perceived unpleasantness of odors, whether or not they are alcohol-related odors.

There are potentially substantial clinical implications of PAE-associated greater perceived relative pleasantness of alcohol beverage odors. It is possible that PAE may mediate increased risk for early initiating of drinking (Sher et al., 1991; Zucker, 1994) or a greater likelihood of alcohol use problems in older teens/young adults with FASDs (Famy et al., 1998) by enhancing the relative hedonic value of alcohol odors. This is consistent with a model of developmental and trans-generational risk for alcohol abuse and alcoholism (Miller & L. Spear, 2006), and preclinical research (e.g., N. Spear & Molina, 2005; Chotro & Arias, 2006; Chotro et al, 2007; Molina et al, 1995), and basic research on mothers and children (e.g., Faas et al, 2000; Mennella & Beauchamp, 1998), reporting more positive reactions to the sensory characteristics of alcohol after PAE. Prior studies have shown that PAE may affect alcohol preference, alcohol-seeking behaviors, and/or alcohol-associated problems in infants, teens or adults (e.g., Alati et al., 2006, 2008; Baer et al., 1998, 2003; Faas et al., 2000; Famy et al., 1998; Yates et al., 1998). It is also possible that in addition to physiological or psychological effects of FASD that might limit the success of interventions for substance use/abuse (e.g., Grant et al, 2013), altered responses to alcohol’s chemosensory cues may also contribute.

While the demonstration of significant associations between PAE and odor perception in young adults is significant with a relatively small sample size, this sample size limits analyses of many factors other than PAE that may also influence perceptions of alcohol odors. Discerning the mechanisms by which PAE may affect odor responses – such as effects on ethanol metabolism, nursing, or infant feeding (e.g., Pueta et al, 2008) – or the influences of other prenatal or postnatal intervening factors that may affect responses to

alcohol odors – such as the young adults’ own drinking, caregiver use, other prenatal and current drug exposures or use, paternal drinking – requires a much larger study. It is important to emphasize that this present correlational study can address neither a cause of differential alcohol odor ratings after PAE, nor the impact of other, potentially important intervening and more proximal factors.

Finally and importantly, in the context of this special issue, the body of work by Distinguished Professor Norman E. “Skip” Spear is foundational to this current research. Dr. Spear’s research on the persistent influence of early learning – whether from the perspective of infantile amnesia or psychopathology or substance use – emphasizes that early experience has a lifelong impact on our perceptions and thinking and behavior and health, even when we are unaware of that experience. More specific to the present paper, the research by Dr. Spear and his colleagues and students since 1984 has demonstrated convincingly, primarily in animal models, that early experiences with alcohol have potent and persistent effects. The fact that many researchers and clinicians are appreciating the important implications of early alcohol experiences for understanding problems ranging from Fetal Alcohol Spectrum Disorders (FASDs) to increased risk for early alcohol use, and problems associated with alcohol use across a lifetime, is due in large measure to Skip’s research and his legacy of “academic progeny” who authored other papers in this volume.

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Highlights

- Subjects from a prospective cohort with known prenatal alcohol exposure are studied
- Hedonic responses to alcohol and other odors were assessed in young adults
- Analyses controlled for other exposures and current drinking
- Prenatal alcohol exposure increased perceived pleasantness of alcohol odors

Table 1

Chemicals Used as Odorants

Nominal	Chemical	Diluent	Concentration
Mint	Carvone	–	100%
Citrus	Citral	mineral oil	10%
Floral	Propionaldehyde	–	100%
Bubblegum	Bubblegum	distilled	50%
Spoiled Milk	Pyridine	water	0.03%
Alcohol	200-proof Alcohol	–	100%
Gin	Beefeater Gin	–	100%
Beer	Rolling Rock	–	100%
Whiskey	Seagram's '7'	–	100%
Water	Water	–	100%

Table 2

Sample Characteristics (N=75)

	Mean or %	SD
Older Teens/Young Adults		
Sex (% male)	38.7%	--
Age (years)	20.9	0.5
TACER-3 Mean Score	0.7	1.1
TACER-3 (% positive – total score = 3)	9.3	--
Tolerance (number of drinks to feel 'high')	1.7	2.5
Tolerance (% = 2 drinks on "T" question)	57.3%	--
Mothers During Pregnancy		
Age at first prenatal visit (years)	26.4	7.2
Cocaine use (% positive)	42.7%	--
Heavy/Persistent* Cocaine use	26.7%	--
Marijuana use (% positive)	33.3%	--
Smoking (# cigarettes/day)	10.0	11.6
ARAE (% positive)	29.3%	--
TACER-3 (% positive)	22.2%	--
Caregivers		
Drinking AA/day at 14-year visit**	0.4	1.1
SES***	27.7	11.3
HOME	51.4	9.2
Education (# years completed)	12.0	1.8

* At least twice/week during pregnancy or positive lab for mother or infant at birth.

** oz. of absolute alcohol/day

*** Socio-Economic Status; Hollingshead, 1975

Table 3

Overall Ratings of Odor Identity, Intensity & Pleasantness

N= 75 unless indicated otherwise		
	Mean	±SD
<i>Odor Identity</i> (Proportion Correct)		
Water	0.77	0.42
Floral	0.13	0.34
Mint	0.89	0.31
Bubble Gum	0.52	0.50
Spoiled Milk	0.20	0.40
Citrus	0.63	0.49
200-proof Alcohol	0.73	0.45
Beer	0.24	0.43
Gin	0.11	0.31
Whiskey	0.35	0.48
Overall Alcohol	0.36	0.21
<i>Odor Intensity</i> (Scale = 1 to 5, less to more)		
Water	1.57	1.02
Floral	3.03	1.04
Mint	3.63	0.90
Bubble Gum	3.17	0.96
Spoiled Milk	3.61	1.17
Citrus	3.59	0.93
200-proof Alcohol	4.29	0.87
Beer	3.41	0.90
Gin	3.31	1.10
Whiskey	3.81	0.98
Overall Alcohol	3.71	0.67
<i>Odor Pleasantness</i> (Scale = 1 to 5, less to more)		
Water (n=33)	3.03	0.73
Floral (n=73)	3.52	1.06
Mint (n=74)	3.82	0.82
Bubble Gum (n=73)	3.88	0.87
Spoiled Milk (n=73)	1.86	1.03
Citrus	3.79	1.06
200-proof Alcohol	1.96	0.99
Beer	2.79	1.15
Gin (n=73)	2.77	1.02
Whiskey	2.47	0.99
Overall Alcohol	2.49	0.66

Table 4

Relations between Alcohol Exposure and Odor Responses

	Prenatal Alcohol Predictor [‡]		
	Prenatal ARAE N=75	Maternal TACER-3 N=60	Maternal TACER-3 [§] N=60
	β	β	β
<i>Odor Identity</i>			
Water	0.08	0.00	0.11
Floral	-0.10	-0.14	-0.07
Mint	-0.03	-0.04	-0.03
Bubble Gum	-0.14	-0.44*	-0.12
Spoiled Milk	-0.14	0.06	-.13
Citrus	-0.03	0.02	-0.01
200-proof Alcohol	0.24 [†]	0.12	-0.25*
Beer	0.06	-0.03	0.06
Gin	0.22	-0.14	0.20
Whiskey	-0.17	-0.23	-0.23 [†]
Overall Alcohol	0.14	-0.04	-.11
<i>Odor Intensity</i>			
Water	-0.03	0.02	-0.08
Floral	0.01	0.06	-0.02
Mint	-0.03	0.21	-.03
Bubble Gum	0.03	-0.18	0.04
Spoiled Milk	-0.08	-0.24	-0.12
Citrus	-0.16	-0.26	-0.18
200-proof Alcohol	0.01	0.10	-0.03
Beer	-0.21	-0.14	-0.23 [†]
Gin	-0.02	0.00	-0.05
Whiskey	0.02	0.12	0.00
Overall Alcohol	-0.07	0.07	-0.16
<i>Odor Pleasantness</i>			
Water	--	--	--
Floral	0.00	-0.02	0.04
Mint	-0.07	-0.01	-0.09
Bubble Gum	-0.03	-0.15	-0.04
Spoiled Milk	0.23 [†]	0.14	0.20
Citrus	-0.12	-0.20	-.12
200-proof Alcohol	0.20	0.05	0.17

	Prenatal Alcohol Predictor [‡]		
	Prenatal ARAE N=75	Maternal TACER-3 N=60	Maternal TACER-3 [✓] N=60
	β	β	β
Beer	0.07	0.23	0.05
Gin	0.28*	0.56**	0.27*
Whiskey	0.18	0.19	0.17
Overall Alcohol	0.34**	0.43**	0.33**

[‡]SIT Total and maternal alcohol use at 14-year visit included as covariate.

[✓]Young Adult Tolerance from TACER-3 added as a covariate.

[†]p = 0.10,

* p = 0.05,

** p = 0.01.

Table 5

Mean Odor Pleasantness

	ARAE	N	Mean	SD	t
Floral	Not at Risk	52	3.54	0.92	0.23
	At Risk	21	3.48	1.36	
Mint	Not at Risk	53	3.85	0.84	0.43
	At Risk	21	3.76	0.77	
Bubble Gum	Not at Risk	51	3.94	0.88	0.97
	At Risk	22	3.73	0.83	
Spoiled Milk	Not at Risk	53	1.74	0.96	-1.74 [†]
	At Risk	20	2.20	1.15	
Citrus	Not at Risk	53	3.83	1.05	0.55
	At Risk	22	3.68	1.09	
200-proof Alcohol	Not at Risk	53	1.89	0.91	-0.99
	At Risk	22	2.14	1.17	
Beer	Not at Risk	53	2.74	1.15	-0.59
	At Risk	22	2.91	1.19	
Gin	Not at Risk	51	2.59	1.00	-2.35[#]
	At Risk	22	3.18	0.96	
Whiskey	Not at Risk	53	2.34	0.96	-1.75 [†]
	At Risk	22	2.77	1.02	
Overall Alcohol	Not at Risk	53	2.38	0.62	-2.25[#]
	At Risk	22	2.75	0.70	