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AN FMRI STUDY OF SPATIAL WORKING MEMORY IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE: CONTRIBUTION OF FAMILIAL HISTORY OF ALCOHOL USE DISORDERS

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Abstract

Background—Heavy prenatal alcohol exposure leads to widespread cognitive deficits, including problems with spatial working memory (SWM). Neuroimaging studies report structural and functional abnormalities in FASD, but interpretations may be complicated by the co-occurrence of a family history of alcoholism. Since, this history is also linked to cognitive deficits and brain abnormalities, it is difficult to determine the extent to which deficits are unique to prenatal alcohol exposure.

Methods—Age-matched subjects selected from two neuroimaging studies, underwent functional imaging while engaging in a task assessing memory for spatial locations relative to a vigilance condition assessing attention. Pairwise comparisons were made for the following three groups: children with histories of heavy prenatal alcohol exposure (ALC, n=18); those with no prenatal alcohol exposure, but a confirmed family history of alcoholism (FHP, n=18); and non-exposed, family history negative controls (CON, n=17).

Results—Relative to CON and FHP, the ALC group showed increased BOLD response in the left middle and superior frontal gyri for the spatial working memory condition relative to the vigilance condition (SWM contrast). Additionally, the ALC group showed unique BOLD response increases in the left lingual gyrus and right middle frontal gyrus relative to CON, and left cuneus and precuneus relative to FHP. Both ALC and FHP showed greater activation compared to CON in the lentiform nucleus and insular region.

Conclusions—These results confirm previous studies suggesting SWM deficits in FASD. Differences between the ALC group and the CON and FHP groups suggest the left middle and superior frontal region may be specifically affected in alcohol-exposed children. Conversely, differences from the CON group in the lentiform nucleus and insular region for the ALC and FHP groups may indicate this region is associated with family history of alcoholism rather than specifically with prenatal alcohol exposure.

Keywords

Fetal Alcohol Spectrum Disorders (FASD); Fetal Alcohol Syndrome (FAS); Functional Magnetic Resonance Imaging; Spatial Working Memory; Family History of Alcoholism

INTRODUCTION

The last 40 years have shown the effects of prenatal exposure to alcohol to be more expansive than originally reported (Jones and Smith, 1973). Fetal alcohol syndrome (FAS) is defined by central nervous system abnormalities, cranio-facial dysmorphology, and pre/post-natal growth deficiencies. Fetal alcohol spectrum disorders (FASD) include individuals with prenatal alcohol exposure with and without FAS (Bertrand et al., 2005). Current estimates of the prevalence of FASD, including FAS, are 2–5% (May et al., 2009, Sampson et al., 1997). A range of behavioral and cognitive impairments has been reported in individuals with FASD, encompassing general intelligence, adaptive function, verbal learning and memory, attention, executive function, and visual-spatial functioning, including spatial and object learning and memory (Kodituwakku, 2007; Mattson et al., 2011; Mattson and Riley, 1998).

Functional magnetic resonance imaging (fMRI) studies of FASD describe blood oxygen level dependent (BOLD) signal differences that may help explain visuospatial deficits reported in the neuropsychological literature (for review, Coles and Li, 2011; Norman et al., 2009). Three fMRI studies have examined spatial working memory (SWM) and offer differing results; however different, all three studies suggest altered patterns of brain response in individuals with FASD compared to non-exposed peers. Alcohol-exposed subjects showed increased BOLD response in inferior and middle frontal regions during a 1-back condition (Malisz et al., 2005) and in frontal, superior and middle temporal, occipital, insular and subcortical areas during a 2-back condition for spatial locations (Spadoni et al., 2009). In a third study, subjects prenatally exposed to alcohol demonstrated less activation in right middle frontal, dorsolateral prefrontal, and posterior parietal cortices when recalling faces (Astley et al., 2009).

Often overshadowed by the more prominent features of prenatal exposure (e.g., facial dysmorphology, IQ deficits), alcohol-exposed individuals are also subject to increased risk for psychiatric disorders, based on family history and genetics (Baer et al., 2003; Barr et al., 2006; Fryer et al., 2007a; Streissguth et al., 2004). Two studies have assessed the role of both prenatal alcohol exposure and familial risk in relation to developmental or psychiatric disorders. These studies reported that individually, each risk contributed to diagnoses, but when accounting for both, familial risk was the leading factor (Hill et al., 2000; Knopik et al., 2005). Additionally, neuropsychological research suggests that youth with a familial history of alcoholism, relative to youth without such histories, show deficits in similar cognitive domains as youth with prenatal alcohol exposure: language, academic achievement, attention and of relevance to the current investigation, measures of visuospatial functioning (Corral et al., 2003; Harden and Pihl, 1995; Hegedus et al., 1984; Ozkaragoz et al., 1997; Poon et al., 2000; Tarter et al., 1997).

One fMRI study has examined SWM and aspects of attention in youth with and without a familial history of alcoholism (Spadoni et al., 2008). Youth with greater familial density (i.e., number of biological parents/grandparents with alcohol use disorders or AUDs), showed less BOLD response during a vigilance condition (lower order task) in medial frontal, cingulate, and posterior cingulate; no BOLD response differences were observed in the SWM condition (higher order task). Thus, it is possible that some previous findings may

be related to family history of AUDs while other findings may be specific to the effects of prenatal alcohol exposure.

The current study compared BOLD response during an SWM task in children with histories of heavy prenatal alcohol exposure, children with family histories of AUDs but not prenatal alcohol exposure, and non-exposed controls without a family history of AUDs. The hypotheses of the study were as follows: (1) children with histories of heavy prenatal alcohol exposure would show more activation in frontal regions for the SWM condition relative to vigilance contrast in comparison to both children with a family history and controls, who would not differ from each other; (2) all groups would show similar activation patterns to the SWM condition (relative to rest) on the higher order task; and (3) children with histories of heavy prenatal alcohol exposure would show less BOLD response than controls when performing the lower order task (i.e., vigilance); the family history and control groups would not differ from each other.

MATERIALS AND METHODS

Subjects

Three groups were included in this study: youth with histories of heavy prenatal alcohol exposure (ALC), youth without prenatal alcohol exposure but with an AUD family history (FHP), and youth with no prenatal alcohol exposure or AUD family history (CON). Fifty-three, right-handed children aged 12–18 years, were selected from two ongoing neuroimaging studies (18 ALC, 17 CON, 18 FHP), one examining the teratogenic effects of alcohol, and one examining family history of AUDs. ALC subjects were recruited by professional or self-referral; the remaining subjects were recruited through the community-at-large.

Across groups, exclusionary criteria included: history of head trauma, neurological disorders, or serious medical problems; MRI contraindications; sensory impairments; primary language other than English; and left-handedness. Additional exclusionary criteria differed by group, with FHP and CON youth excluded for prenatal substance exposure (i.e., >2 drinks per week and any substance use), psychiatric illness and psychoactive medications. Given the high rates of psychiatric diagnoses in FASD (e.g., Fryer et al., 2007a), their presence was not exclusionary in the ALC group.

For inclusion in the ALC group, youth were confirmed to have histories of heavy prenatal alcohol exposure as evidenced from multiple sources (i.e., medical, social service, and adoption agency records and when available, maternal report). Heavy prenatal alcohol exposure was defined as the mother consuming at least four drinks per occasion, at least once a week, or 14 or more drinks per week. All subjects in this group were evaluated by a dysmorphologist (KLJ), an expert in the diagnosis of FAS. The ALC group included seven children with FAS. Family history of AUDs was assumed in the ALC group based on the presence of heavy prenatal alcohol exposure. However, because the majority of the current ALC sample resided with non-biological family members, maternal abuse or dependence diagnoses and the extent of family history (i.e., paternal, grandparents) could not be confirmed. For inclusion in the FHP group, biological parents' and grandparents' abuse or dependence histories were evaluated through parental and youth reports, with a diagnosis on any one report needed for inclusion. CON subjects could not meet criteria for either of the other two groups. A subset of subjects were included in our previous studies of FASD and FHP (Spadoni et al., 2009; Spadoni et al., 2008).

Each subject's Full Scale IQ (FSIQ) score was assessed using either the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) or the Wechsler Intelligence

Scale for Children (WISC-III, WISC-IV) (Wechsler, 1991; Wechsler, 2004). Socioeconomic status (SES) was assessed using the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). Groups were matched on age, sex, and SES.

Child assent and parental or caregiver informed consent was obtained prior to participation. Procedures were approved by the Institutional Review Board at San Diego State University and the University of California, San Diego. Subjects received compensation for their time.

Procedure

Experimental Measure—The experimental task (see Figure 1), originally adapted from McCarthy and colleagues (1994), and subsequently modified (Kindermann et al., 2004; Tapert et al., 2001), has previously been used to probe brain regions subserving SWM in populations with family history of alcoholism and prenatal alcohol exposure (Spadoni et al., 2009; Spadoni et al., 2008). Eighteen alternating blocks of the SWM condition and a baseline vigilance condition, each lasting 20 seconds, were dispersed around resting fixation periods at the beginning, middle and end of the experiment. Both conditions consisted of 10 designs (Kimura figures; Kimura, 1963) appearing in one of eight set locations. Stimuli were presented for 1000ms, with a 1000ms inter-stimulus interval (ISI). Performance and reaction times were recorded using the subject's right index finger for the SWM condition when a figure appeared in the same location as the figure shown two trials earlier (2-back) and for the vigilance condition when a dot appeared above a figure.

Image Acquisition—Structural and functional images were acquired at the University of California, San Diego Center for Functional Magnetic Resonance Imaging (CFMRI) on a 3-Tesla General Electric CXK4 short bore Excite-2 MR system (Milwaukee, WI) whole body system with an 8-channel phase-array head coil. A high-resolution structural image was collected sagittally and used for co-registration with the functional protocol: TR=7.8 ms, TE=3 ms, flip angle=12°, 256×192 matrix, 1mm slice thickness, FOV=24 cm, and acquisition time 7:24. Functional images were collected axially using echo planar imaging: TR=3000 ms, TE=32 ms, flip angle=90°, 3.43 mm x 3.43 mm, 3.8 mm slice thickness, and acquisition time=7:48.

Statistical Analyses—Group comparisons of demographic variables were analyzed by Chi-square for sex and race/ethnicity, analysis of variance (ANOVA) for age, FSIQ, and SES and when significant, were followed up with pairwise comparisons.

Accuracy and reaction times were analyzed separately using three one-way ANOVAs for group comparisons (ALC to CON, ALC to FHP, FHP to CON). To ensure task attention and understanding, subjects were excluded from analysis if their accuracy scores were below 69% for either condition (Spadoni et al., 2009). Any behavioral differences during the SWM condition were followed up using a one-way ANCOVA with group as the independent variable, SWM accuracy or reaction time as the dependent variable, and vigilance accuracy and reaction time as covariates.

Imaging data were processed using Analysis of Functional NeuroImages (AFNI; afni.nimh.nih.gov; Cox, 1996) by analysts blind to group status. Motion within the time series was corrected by registering each acquisition to a minimally deviant repetition (Cox and Jesmanowicz, 1999; Paulus et al., 2004). Motion correction parameters (3 displacement, 3 rotational) were recorded for each subject. Further, visible motion within the series was censored from further analysis. Data were excluded from analysis if greater than 20% of a subject's repetitions were censored (ALC=1, CON=1 not described in this study). Mann-Whitney U tests compared groups on the number of removed repetitions, and bulk and task correlated motion.

Time series data underwent deconvolution using a gamma variate reference function specific to the alternating presentation of task conditions (SWM, vigilance, fixation) (Ward, 2002) and modeled hemodynamic response (Boynton et al., 1996; Cohen et al., 1997), while covarying for all six motion correction parameters and linear trends (Bandettini et al., 1993). The end result was a single, fit coefficient representing BOLD response for the SWM condition relative to the vigilance condition, for each voxel within the brain. Functional data were transformed into standard space (Talairach and Tournoux, 1988), resampled into 4.0 mm³ voxels, and spatially smoothed with the application of a Gaussian filter (full-width half maximum = 5.0 mm).

Single sample *t*-tests examined overall activation patterns by group (ALC, FHP, CON) and condition (SWM, vigilance). Group comparisons of BOLD response for the SWM/vigilance contrast and each condition (SWM, vigilance) were performed using independent samples *t*-tests (AFNI; 3dttest). All pairwise comparisons were performed: ALC to CON, ALC to FHP, and FHP to CON. A combination of *t* statistic magnitude and cluster volume thresholding ($p < .01$, clusters = 1024 μ l) were used to control for Type I error (Forman et al., 1995, Ward 1997). BOLD response data for the resulting clusters, were exported to SPSS for further analysis and outlier discrimination. To further examine the effect of group differences on BOLD response, three one-way analyses of covariance (ANCOVAs) were performed with group (ALC, FHP, CON) as the independent variable, measures of BOLD response as the dependent variables, and measures that may have contributed to differences in BOLD response such as age, accuracy, reaction time, and FSIQ as covariates.

RESULTS

Demographics

The groups were similar in age, SES, sex, and race ($p > .05$). Groups differed on ethnicity (χ^2 (df=2)=7.782, $p=.020$), and FSIQ ($F(2, 51)=10.388$, $p<.001$). For ethnicity, neither the ALC or FHP groups differed significantly from the CON group, but the ALC group had significantly ($p<.05$) fewer Hispanic subjects than the FHP group. For FSIQ, the CON and FHP groups each had significantly greater FSIQ than the ALC group. Demographic information is presented in Table 1.

Behavioral Data

Response logging failed for five subjects (3 ALC, 2 FHP); behavioral analyses and fMRI analyses using behavioral measures as covariates were run with the remaining subjects. During vigilance, the ALC group responded less accurately than both the CON ($F(1,30)=6.296$, $p=.018$) and the FHP groups ($F(1,29)=6.167$, $p=.019$). The ALC group also responded at a slower rate than the CON group ($F(1,30)=4.865$, $p=.035$) and the FHP group ($F(1,29)=4.769$, $p=.037$). For the SWM condition, the ALC group was less accurate than the CON group ($F(1,30)=7.020$, $p=.013$), but not significantly different from the FHP group ($F(1,29)=0.985$, $p=.329$). When accounting for vigilance performance (accuracy and reaction time), SWM accuracy was no longer significantly different between the ALC and CON groups ($F(1,28)=1.635$, $p=.212$). The ALC group did not differ from either group (CON or FHP) on reaction time to the SWM condition. There were no significant differences ($p > .05$) between the FHP and CON groups in accuracy or reaction time for either the vigilance or SWM condition. Correlations between task accuracy and subsequent fMRI BOLD response differences across and within groups were non-significant ($p > .05$).

For SWM, both CON (Pearson $r=.510$; $p<.05$) and FHP (Pearson $r=.498$; $p=.05$) groups demonstrated better accuracy with increasing FSIQ. This relationship was not seen in the

ALC group. There were no significant correlations between FSIQ and vigilance performance.

fMRI Analysis

Each groups' general pattern of activation across conditions and contrasts was examined with single sample *t*-tests ($p < .01$, clusters $> 1024 \mu\text{l}$); see Table 2 and Figure 2. All groups showed activation bilaterally across the frontal gyrus, anterior cingulate, precuneus, and the parietal lobe, all expected regions of BOLD response during tasks of working memory and attention (Nelson et al., 2000; Spadoni et al., 2007; Spadoni et al., 2008; Thomas et al., 1999). However, the ALC group showed generally fewer regions of activity, with relatively limited frontal activation in comparison to both the CON and FHP groups. Further qualitative review showed this limited frontal activity was primarily due to the ALC group's absence of frontal BOLD response during the vigilance condition. Though limited in overall BOLD response during both SWM and vigilance, the magnitude of activation within significant regions was generally greater than the CON and FHP groups.

ALC/CON Comparison

An independent samples *t*-test revealed four clusters where the ALC group, in comparison to the CON group, showed significantly more ($p < .01$) BOLD response for the SWM relative to the vigilance contrast: left middle and superior frontal gyrus, lingual gyrus and cuneus, lentiform nucleus and insula, and the right middle frontal gyrus. There were no clusters in which the ALC group showed less BOLD response than the CON group for the SWM contrast. To control for potential differences in SWM processing (accuracy and reaction time) across age and FSIQ, data were reanalyzed using ANCOVA with task behavioral measures, age, and FSIQ as covariates. All four clusters remained significant above and beyond their effects. One cluster, encompassing the left lingual gyrus, was negatively correlated with FSIQ (Pearson $r = -0.407$, $p = .017$) across both groups. When examining the SWM and vigilance conditions individually, the ALC group showed significantly less BOLD response in the medial temporal gyrus than the CON group in both conditions.

ALC/FHP Comparisons

An independent samples *t*-test revealed two clusters where the ALC demonstrated greater BOLD response ($p < .01$) to the SWM contrast than the FHP group: left middle frontal gyrus and right cuneus and precuneus. For the SWM contrast, there was no significant clusters where the ALC group showed less BOLD response than the FHP group. Both clusters remained significant after accounting for task behavioral measures, age, and FSIQ. Analyses examining SWM and vigilance individually, revealed decreased BOLD response in the ALC group relative to the FHP during vigilance in one cluster (i.e., right cuneus and lingual gyrus)

The ALC group showed significantly more movement than the FHP group ($p < .05$) for bulk and task-correlated motion in the superior direction. All analyses were repeated and remained significant ($p < .01$) after accounting for these motion parameters.

FHP/CON Comparisons

An independent samples *t*-test indicated two clusters where the FHP group showed greater BOLD response than the CON group for the SWM contrast: left lentiform nucleus and insula, and right thalamus. Analyses remained unchanged after accounting for task behavioral measures, age, and FSIQ. No significant group differences emerged for the individual SWM and vigilance conditions.

Follow-up Analyses

Three regions where the ALC group demonstrated greater BOLD response for the SWM contrast relative to the CON group were further examined: left middle/superior frontal, left lingual gyrus/cuneus, and left lentiform nucleus/insula. Under qualitative review, two of these regions appear in other comparisons, ALC vs. FHP (left middle frontal) and FHP vs. CON (left lentiform nucleus/insula). SWM relative to vigilance values for these three regions ($p < .01$, clusters $> 1024 \mu\text{l}$), as defined by the ALC and CON comparison, were extracted and exported to SPSS (see Figure 3). Three one-way ANOVAs, one for each region of interest, showed a main effect of group and were followed by Tukey post-hoc comparisons: left middle frontal ($F(2,50)=19.195$, $p < .001$), left lingual gyrus/cuneus ($F(2,50)=5.669$, $p = .006$), and the left lentiform nucleus/insula ($F(2,50)=9.830$, $p < .001$). Results were consistent with the three independent samples t -tests performed within AFNI. For the left middle frontal regions the ALC group demonstrated significantly greater BOLD response in comparison to both the CON and FHP groups ($p < .001$). Similarly, in the left lentiform nucleus and insular region, both the ALC ($p < .001$) and FHP ($p = .022$) groups demonstrated greater BOLD response than the CON group. Additionally, the ALC group showed greater BOLD response compared to controls in the left lingual gyrus/cuneus ($p = .005$). All other comparisons were nonsignificant ($p > .05$).

DISCUSSION

The current study compared spatial working memory in children with histories of heavy prenatal alcohol exposure, those without a history of prenatal alcohol exposure, but with a family history of AUDs, and non-exposed controls without a history of prenatal alcohol exposure or a family history of AUDs. Given the potential confound of family history of AUDs within the FASD population, understanding the unique contribution of prenatal alcohol exposure versus a family history of AUDs is vital to interpretation and implications of current FASD neuroimaging research.

In support of our first hypothesis, the ALC group demonstrated more activation than both comparison groups in the left middle and superior frontal gyrus, and the right middle frontal gyrus. The ALC group also showed unique increased activation for the SWM contrast in non-frontal regions, including the left lingual gyrus, and lentiform nucleus and insular region in comparison to the CON group and the right cuneus and precuneus in comparison to the FHP group. These results are consistent with aberrant function in frontal, parietal, and occipital cortices reported in previous fMRI studies of FASD (Astley et al., 2009; Fryer et al., 2007b; Li et al., 2008; O'Hare et al., 2009; Sowell et al., 2007; Spadoni et al., 2009). While studies of SWM in FASD report similar increases in frontal BOLD response, they show varying degrees of behavioral differences (Malisza et al., 2005; Spadoni et al., 2009). In the presence of equivalent task performance, increased BOLD response may indicate less efficient functional processing, but with performance differences present, greater BOLD activation may imply neural compensation for other less active regions. The latter explanation can be supported by studies reporting significant increased activation in frontal areas, coupled with decreased activation in the caudate nucleus during a task of inhibition (Fryer et al., 2007b) and in the medial temporal lobe during verbal learning (Sowell et al., 2007). While the current study did not report significant decreases in BOLD response between groups, within-subject analyses of the SWM contrast in the ALC group revealed smaller clusters of significant activation and fewer BOLD response clusters relative to the other two groups. Similar qualitative findings, despite a lack of significant group findings, was also reported in Fryer et al. (2007b). Despite generally fewer significant regions of SWM activity in the alcohol-exposed children, greater intensity of BOLD response in the significant clusters relative to the other groups offers further support for a compensation hypotheses. Thus, children with prenatal alcohol exposure may require more neural effort

from limited recruited regions to compensate for less diffuse BOLD activation seen in comparison to both those with a family history of AUDs and controls.

Contrary to our first hypothesis, both ALC and FHP groups, relative to CON, showed greater activation to the SWM contrast in the lentiform nucleus (i.e., putamen) and insular region. Significant activation of the lentiform nucleus and insular regions has been reported in other studies of SWM (Malisza et al., 2005; Scherf et al., 2006; Spadoni et al., 2009). The experimental task design may offer an explanation for similar results across the ALC and FHP groups. The lentiform nucleus (i.e., putamen, globus pallidus) may be preferentially activated in spatial working memory paradigms in which subjects can use an “egocentric” strategy, such that they can remember the target stimulus in relation to themselves (Postle and D’Esposito, 2003). The current study utilized such a paradigm and results indicate that children with prenatal alcohol exposure and those with a familial history of AUDs may have relied on this strategy, and thus require more neural effort from this region.

Alternatively, increased BOLD response in the lentiform nucleus and insula for the ALC and FHP groups may be associated with familial risk for AUDs and not specifically linked to prenatal alcohol exposure. However, a separate investigation using this same SWM task in youth with a family history of AUDs reported no group differences in the lentiform nucleus and insular region (Spadoni et al., 2008). Regional differences in the lentiform nucleus and insular region across comparisons may also suggest these regions are not associated with family history, but rather underlying traits common to both the ALC and FHP groups. Structurally, the insular region has been implicated in childhood behavioral disorders, such as conduct disorder and oppositional defiant disorder (Fahim et al., 2011), both of which occur at higher rates in alcohol-exposed children and those with a family history of substance use (Fryer et al., 2007a; Hill et al., 2000).

While the SWM contrast explores differences in SWM beyond the role of attention, it does not address significant differences within each condition. During the SWM condition no significant group differences in BOLD response were found in the ALC versus FHP and FHP versus CON comparisons. Contrary to our hypothesis, relative to controls, the ALC group showed decreased BOLD response in the left middle temporal region during the SWM condition. One other study of FASD has shown reduced BOLD response of the medial temporal lobe during a task of verbal learning (Sowell et al., 2007). Given increased frontal BOLD response within their sample, the authors suggested that alcohol-exposed subjects may rely on frontal memory systems for verbal encoding and retrieval. In support of this interpretation, magnetoencephalography studies of working memory suggest the medial temporal lobe is specifically recruited during the encoding processes in both tasks of verbal and spatial working memory (Campo et al., 2005). Thus, aberrant medial temporal functioning during SWM in FASD may also be related to deficits in encoding.

Finally, we predicted that the ALC group would use less attentional resources than the other groups. Contrary to this hypothesis, the ALC group showed increased BOLD response in the superior frontal gyrus relative to controls, a region not found to differ between the groups for the SWM relative to vigilance contrast. Additionally, the FHP group demonstrated greater BOLD response than the ALC and CON groups during the vigilance condition in the right cuneus and lingual gyrus. Greater BOLD response during vigilance may suggest that both groups (ALC, FHP) are recruiting additional resources needed to maintain an adequate (i.e., above chance) level of attention. For the FHP group, this level of attention as suggested by accuracy scores is greater than the ALC group and comparable to controls, however, those with prenatal alcohol exposure may be using more neural resources and still underperforming relative to both control groups (CON, FHP). The ALC group also demonstrated less BOLD response in the medial temporal region during the vigilance

condition than the CON group. Research suggests early activation of the medial temporal lobe may be a result of attention (Campo et al., 2005; Martin, 1999). Although timing of activation is difficult to interpret in fMRI studies, the potential role of the medial temporal lobe in attention fits the current data, suggesting decreased medial temporal BOLD response in the ALC group may be associated with less accurate responses during vigilance.

Beyond the differences observed in BOLD response, children with prenatal alcohol exposure exhibited poorer accuracy during both task conditions (SWM, vigilance), as well as slower reaction time during the vigilance condition. The ALC group also exhibited significantly lower IQ scores, a finding consistently reported in the larger FASD population. No relationship between IQ and behavioral accuracy was seen for the vigilance or SWM conditions in the alcohol-exposed group. In contrast, the other groups (CON, FHP) showed increased accuracy with increasing FSIQ scores during the SWM condition. The lack of relationship seen in the ALC group suggests attention and SWM deficits are present above any deficits resulting from low IQ.

Despite these novel findings, several limitations should be considered. First, subjects were from two independent research groups; interpretations should consider the potential that inherent study differences contributed to group differences. Subjects across both studies were asked to refrain from stimulant and psychoactive medications. However, due to increased rates of comorbid disorders within the FASD population, medication withdrawal within the alcohol-exposed group was not always possible and exclusion of such subjects may hinder the generalizability of the findings. Second, while family history of AUDs within the ALC group is assumed, there may be a varying degree of family history of AUDs within the alcohol-exposed group and ultimately across the sample as a whole. Finally, while age did not correlate with any behavioral or fMRI measures in this study, maturational differences in spatial working memory and BOLD response patterns across the wide age range (12–18 years) could affect interpretation of results.

This is the first study to investigate the contribution of a family history of alcohol use disorders in brain functioning of children with histories of heavy prenatal alcohol exposure. Differences across all three comparisons suggest a graded effect such that the ALC and CON comparison showed the greatest number of group differences, with less significant differences found between ALC and FHP subjects and FHP and CON subjects. Disparities in neural functioning between the ALC group and both comparisons (FHP, CON) confirm previous reports of altered spatial working memory functioning in alcohol-exposed children and suggest that alterations in the left middle and frontal gyrus were not due to family history of AUDs. BOLD response differences in the lentiform nucleus and insular regions for both family history groups (ALC, FHP) compared to controls suggest the neural abnormalities in alcohol-exposed children may be two-fold, resulting from both prenatal alcohol exposure and family history.

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Figure 1.
Spatial Working Memory Task consisting of three conditions: fixation (look); vigilance (dots); and spatial working memory (where).

Figure 2. BOLD response differences ($p < .01$, clusters $\geq 1024 \mu l$) for the SWM condition relative to the vigilance condition for all three comparisons. Orange areas indicate greater BOLD response.

Figure 3.

Difference in BOLD response (i.e., beta weights) for the SWM relative to vigilance contrast for three regions of interest: left middle frontal, left lingual gyrus/cuneus, and left lentiform nucleus/insula. Data are presented as mean $\pm$ standard error of the mean.

Table 1

Demographic information for children with histories of heavy prenatal alcohol exposure (ALC), children with no prenatal alcohol exposure, but with a confirmed family history of alcohol use disorders (FHP), and controls (CON)

	ALC*	FHP	CON	Significant pairwise comparisons ^b
N	18	18	17	
Sex [N (%) Female]	4 (22.2)	6 (33.3)	9 (47.1)	
Race [N (%) White]	12 (66.7)	8 (44.4)	9 (52.9)	
Ethnicity [N (%) Hispanic] ^b	3 (16.7)	11 (61.1)	6 (35.3)	
Age in years [M (SD)]	15.1 (1.9)	14.9 (1.8)	15.0 (1.9)	
SES [M (SD)]	47.1 (10.1)	41.9 (17.2)	50.1 (14.8)	
FSIQ [M (SD)]	88.5 (12.2)	105.9 (14.3)	107.4 (15.4)	ALC vs. CON, ALC vs. FHP
Vigilance Accuracy [M (SD)] ^a	93.4 (4.9)	96.8 (2.3)	96.5 (1.6)	
Vigilance Reaction Time [M (SD)] ^a	688.9 (79.0)	632.6 (64.1)	636.5 (54.4)	ALC vs. CON, ALC vs. FHP
SWM Accuracy [M (SD)] ^a	84.7 (11.3)	91.1 (6.7)	93.1 (6.2)	ALC vs. CON
SWM Reaction Time [M (SD)] ^a	562.9 (116.1)	607.5 (133.3)	564.6 (76.6)	

* ALC group includes FAS (N=7)

^a ALC (N=15), FHP (N=16), CON (N=17)

^b significance levels set at $p < .05$

SWM contrast results (SWM-vigilance): clusters showing significantly greater BOLD response (each cluster was 16 contiguous voxels, 1024 μ l, with each voxel differing at $\alpha < .01$)

Table 2

Anatomical region	Effect Size Cohen's <i>d</i>	Brodmann Area	Volume (μl)	x	y	z
ALC > CON						
L middle and superior frontal gyrus	1.73	8, 9	2240	34	-27	40
L lingual gyrus and cuneus	1.54	17, 18	1408	18	93	-4
L lentiform nucleus and insula	1.40		1280	38	1	-4
R middle frontal	1.26	8, 9	1152	-38	-19	44
ALC > FHP						
L middle frontal gyrus	1.59	8	1920	34	-27	40
L cuneus and precuneus	1.51	31, 18	1728	-2	77	32
FHP > CON						
L lentiform nucleus and insula	1.59		1344	-30	-3	-8
R thalamus	1.51		1344	-2	29	0

R *right*; L *left*

^aCoordinates refer to the location of the peak group difference within the cluster