Prenatal Alcohol Exposure Affects Frontal–Striatal BOLD Response During Inhibitory Control

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Background: Prenatal alcohol exposure can lead to widespread cognitive impairment and behavioral dysregulation, including deficits in attention and response inhibition. This study characterized the neural substrates underlying the disinhibited behavioral profile of individuals with fetal alcohol spectrum disorders (FASD).

Methods: Children and adolescents (ages 8–18) with (n = 13) and without (n = 9) histories of heavy prenatal alcohol exposure underwent functional magnetic resonance imaging while performing a response inhibition (go/no-go) task.

Results: Despite similar task performance (mean response latency, performance accuracy, and signal detection), blood oxygen level-dependent (BOLD) response patterns differed by group. Region-of-interest analyses revealed that during portions of the behavioral task that required response inhibition, alcohol-exposed participants showed greater BOLD response across prefrontal cortical regions (including the left medial and right middle frontal gyri), while they showed less right caudate nucleus activation, compared with control participants.

Conclusions: These data provide an account of response inhibition-related brain functioning in youth with FASD. Furthermore, results suggest that the frontal–striatal circuitry thought to mediate inhibitory control is sensitive to alcohol teratogenesis.

Key Words: Fetal Alcohol Spectrum Disorders, Response Inhibition, Functional Neuroimaging, Fetal Alcohol Syndrome.

Although fetal alcohol syndrome (FAS) has been clinically recognized for decades, it is now acknowledged that prenatal alcohol exposure can be associated with cognitive and behavioral deficits, even in the absence of the facial features and physical growth retardation required to make a diagnosis of FAS. Accordingly, fetal alcohol spectrum disorders (FASD) is used as an umbrella term to describe the range of effects attributable to gestational alcohol exposure. The incidence of FASD has been conservatively estimated at 9 per 1,000 live births (Sampson et al., 1997). Individuals with histories of heavy prenatal alcohol exposure may present with a range of cognitive dysfunctions, including deficits in general intelligence, attention, learning, memory, visuo-spatial cognition, and psychomotor skills (Autti-Rämö, 2000; Mattson and Riley, 1998; Streissguth et al., 2004).

Executive functioning (EF) is a heterogeneous neuropsychological concept encompassing integrative higher-order cognitive abilities that include behavioral inhibition, working memory, planning, and set shifting (Pennington and Ozonoff, 1996). Anecdotally, individuals with histories of prenatal alcohol exposure are described as lacking in EF-based skills. For example, they may exhibit poor judgment, show impairments in planning and problem solving, or fail to anticipate the consequences of their actions. Neuropsychological assessment has demonstrated deficits in individuals with prenatal alcohol exposure histories across various EF abilities including cognitive planning and flexibility (Kodituwakku et al., 1995; Mattson et al., 1999), and it has been suggested that at least some of the EF deficits associated with prenatal alcohol exposure occur above and beyond general intellectual deficits (Connor et al., 2000).

A task that taps response inhibition was chosen for the present study, because the disinhibited, disruptive behavioral profile reported in individuals with FASD contributes to dysfunction in school, employment, and social settings. Impairment in response inhibition, an aspect of EF, has been proposed as a potential mechanism underlying disruptive behavior disorders (Nigg, 2003; Sergeant et al., 2002). This theoretical framework may be useful in considering the effects of prenatal alcohol exposure, as inattention and misconduct are frequently observed in...
this population. Studies examining psychopathology in individuals with FASD have observed increased rates of disruptive behavior disorders (Fryer et al., 2007; Steinhausen et al., 1993) and antisocial personality traits (Barr et al., 2006). Additionally, individuals prenatally exposed to alcohol may exhibit disruptive or impulsive behaviors that can result in negative consequences such as disrupted schooling, legal problems, inappropriate sexual behavior, and substance abuse (Streissguth et al., 2004).

Response inhibition, a key component of cognitive control, is conceptualized as the ability to suppress irrelevant stimuli or behavioral impulses to facilitate efficient, goal-directed behavior. Response inhibition is often measured by errors of commission on tasks where the goal is to inhibit a prepotent response. Although the development of complex behavioral phenomena, such as response inhibition, is widely acknowledged to be multifactorial, neuropsychological assessment suggests that response inhibition ability is sensitive to alcohol teratogenesis. For example, a study using the Delis–Kaplan Executive Function Scale’s Color–Word Interference Test, a modified Stroop task, indicated deficits in children with heavy prenatal alcohol exposure, compared with their peers (Mattson et al., 1999). Task component analysis revealed that the lower performance of the alcohol-exposed group was best accounted for by a response-inhibitory deficit, rather than by impairment on more basic task components such as color naming or reading. Similarly, Stroop performance in adults was among the variables within an EF test battery most strongly associated with prenatal alcohol exposure, and this association was independent of IQ (Connor et al., 2000). Rodent models of prenatal alcohol exposure have also provided an indication that ethanol teratogenesis leads to increased behavioral disinhibition (Barron and Riley, 1990; Gallo and Weinberg, 1982; Riley et al., 1979), and results from animal and human studies of FASD are generally in accordance across many cognitive findings, including response inhibition deficits (Driscoll et al., 1990). Although the weight of evidence suggests that heavy prenatal alcohol exposure is associated with diminished response inhibition, one study did not observe alcohol exposure-associated performance deficits in children on a modified go/no-go task (Kodituwakku et al., 1995).

Convergent evidence from functional neuroimaging, animal model, and human lesion studies indicates that prefrontal cortical regions support response-inhibitory functions (Aron and Poldrack, 2005; Iversen and Mishkin, 1970). Given that well-defined “frontal–subcortical loops” link the basal ganglia to the frontal lobes (Lichter and Cummings, 2001; Middleton and Strick, 2000), subcortical modulation of response inhibition is also posited. One theoretical model has emphasized the role of frontal–striatal connectivity in maintaining inhibitory aspects of cognitive control (Casey et al., 2002), and subcortical lesions have been shown to be sufficient to cause response inhibition deficits in animal models (Thompson et al., 1985). Functional neuroimaging has revealed abnormalities in frontal–striatal blood oxygen level-dependent (BOLD) response in populations with inhibitory deficits, such as fragile X syndrome (Menon et al., 2004), Williams syndrome (Mobbs et al., 2006) and attention-deficit hyperactivity disorder (ADHD) (Durston, 2003; Vaidya et al., 2005). However, other researchers have argued that more reliable response inhibition-related functional activity is localized to right inferior frontal regions, arguing against a prominent role for the striatum (Aron and Poldrack, 2005).

Prior neuroimaging studies of individuals with FASD have described changes in the frontal–subcortical circuitry associated with the regulation of response inhibition, including caudate nucleus volume reduction (Mattson et al., 1996), and anterior and orbital frontal cortical shape abnormalities in alcohol-exposed children (Sowell et al., 2002). Moreover, there is evidence that the caudate volume reductions observed in alcohol-exposed individuals relate to EF deficits. A preliminary study found that caudate volume predicted alcohol-exposed children’s performance as measured by perseverative errors on a test of cognitive flexibility and false-positive errors on a test of learning and memory (Mattson et al., 2001). Neuroimaging techniques have also revealed metabolic abnormalities in the striatum including glucose metabolism reductions (Clark et al., 2000), and elevated N-acetyl-aspartate concentration (Cortese et al., 2006) in individuals with FASD.

The present study used a standard behavioral inhibition task (go/no-go) to examine neural resource allocation underlying putative response inhibition deficits associated with prenatal alcohol exposure. Functional magnetic resonance imaging (fMRI) was performed while children with and without histories of prenatal alcohol exposure completed a go/no-go task. Compared with their typically developing peers, we expected alcohol-exposed individuals to have a greater number of commission errors on aspects of the task that require response inhibition (no-go stimuli), and that between-group BOLD activation differences would be observed within frontal–striatal brain regions. More specifically, based on a review of the pediatric clinical neuroimaging response inhibition literature, we expected to observe between-group BOLD response differences in the lateral prefrontal cortices, the anterior cingulate gyrus, and the striatum (Aron and Poldrack, 2005; Bush et al., 2005; Casey et al., 2002; Rubia et al., 1999). Also, we expected to observe group differences in inferior parietal areas, as there is evidence that this brain region is a target of alcohol teratogenesis (Sowell et al., 2002), and parietal involvement has been elicited by this task in healthy adults (Rubia et al., 2001). As this is the first fMRI study of response inhibition in this population, we did not have an a priori hypothesis about the direction of expected between-group activation differences. However, increased frontal lobe and decreased striatal BOLD response might be expected, based on frontal–striatal...
findings in ADHD samples (Durston et al., 2003; Vaidya et al., 1998).

**MATERIALS AND METHODS**

**Subject Recruitment and Inclusion**

The sample described in this study consists of children and adolescents with heavy prenatal alcohol exposure (ALC; \( n = 13 \)) and typically developing control peers (CON; \( n = 9 \)). Participants were drawn from a retrospective cohort of children with histories of prenatal alcohol exposure who are being followed by the Center for Behavioral Teratology (CBT), San Diego State University (see Mattson et al., 2006 for ascertainment methods). Study inclusion criteria required that subjects be between the ages of 8 and 18, right-handed, and native English language speakers. Potential participants were excluded if they met one or more of the following criteria: a history of head trauma, contraindication for MRI scanning (e.g., metallic implants in the body), claustrophobia, serious medical conditions (e.g., epilepsy), or sensory problems that would interfere with the subject’s ability to perform the task. Additionally, CON subjects were excluded if they had a diagnosis of a psychiatric illness or were taking psychoactive medication. Eight of the 13 ALC subjects were on routinely prescribed psychoactive medication at the time of brain scanning. Medication type included atomoxetine, antidepressants (e.g., sertraline, desipramine), and antipsychotics (e.g., rispiridone, quetiapine). Based on caregiver report, there was no indication of clinically significant substance use within our sample. Of the total potential participants who were screened for this study, 32% were excluded. The most common reason for exclusion was orthodontic braces or other dental implants.

All subjects in the ALC group were previously evaluated by a dysmorphologist with expertise in alcohol teratogenesis (Dr. Kenneth Lyons Jones). The ALC group was composed of children with documented histories of heavy prenatal alcohol exposure, both with \(( n = 6 )\) and without \(( n = 7 )\) FAS. Children with alcohol exposure were recruited by the CBT via referral from Dr. Jones and other medical providers, or were self-referred. Participants in the CON group were self-referred or recruited via community outreach, and were selected to be demographically similar to ALC participants on age, socioeconomic status, and sex, but not on the presence of psychiatric symptoms or IQ, as cases of heavy prenatal alcohol exposure often present with psychopathology and/or cognitive deficits (see Table 1). Intelligence testing was conducted using the Wechsler Intelligence Scale for Children, III (Wechsler, 1991), and the IQ scores of study participants ranged from 73 to 128. Before the neuroimaging session, written informed parental consent and child assent were obtained via protocols approved by the Institutional Review Boards of San Diego State University and University of California, San Diego (UCSD). Subjects were provided with a financial incentive for participation.

**Task Description**

One hundred eighty trials were presented with interspersed baseline rest periods (visual fixation). The stimuli consisted of large circles \(( n = 64 )\), small circles \(( n = 16 )\), large squares \(( n = 43 )\), and small squares \(( n = 57 )\). Each stimulus appeared for 200 ms, with an intertrial interval of 1,500 ms, and interspersed rest periods of 0 to 40 seconds. Subjects were instructed to press a button each time the large circle, small circle, or large square appeared (go stimuli), and not to press the button when the small square was shown (no-go stimulus). During the fixation trials, subjects were instructed to passively look at a plus sign that appeared in the center of their visual field. See Fig. 1 for example task stimuli.

**Data Analysis**

Analysts blind to group classification processed fMRI data using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996; Cox and Hyde, 1997). Image preprocessing included visual inspection of time series data for gross movement artifacts. Data were not included in the analyses if more than 15% of repetitions were judged by 2 independent raters to have excessive, visually discernable, movement (data from 2 ALC and 5 CON subjects not described in this report were excluded, due to excessive movement). To correct small movements over time, image repetitions were registered to a selected...
base volume using the AFNI 3D volume registration program (Cox and Jesmanowicz, 1999). This procedure provided 3 rotational (roll, pitch, yaw) and 3 translational (superior-to-inferior, left-to-right, posterior-to-anterior) parameters for each repetition for each participant, indicating the motion adjustments applied to the time series data. Data were then deconvolved with a task reference vector while modeling the degree of motion correction applied (Bandettini et al., 1993). This yielded per-voxel fit coefficients corresponding to BOLD response specific to task stimulus type. Image data were normalized to stereotaxic space (Talairach and Tournoux, 1988), resampled to 4 mm³ isotropic voxels, and spatially smoothed with a 5 mm full-width at half-maximum Gaussian filter to mitigate neuroanatomical variation among individuals and facilitate group-level analyses.

Planned between-group comparisons (ALC vs CON) examined BOLD response differences between no-go trials (small square) and go trials (all other shapes). These group-wise analyses were conducted using independent samples t-tests with an unpooled error estimate. Two types of between-group analyses were conducted: (1) a hypothesis-driven region-of-interest (ROI) analysis focused on the prefrontal cortex and the caudate nucleus and (2) a whole-brain analysis. For the ROI-based analyses, the prefrontal cortex was manually defined to include all brain tissue anterior to the genu of corpus callosum, while the caudate nucleus was defined using Talairach Daemon software (Lancaster et al., 2000).

Type I error was controlled at an experiment-wise rate of 0.05 by setting a voxel significance threshold (p < 0.05) and cluster volume threshold based on the size of the overall area of analysis. The size of the cluster threshold was determined by a Monte-Carlo simulation-based algorithm using a 4 mm connectivity radius to define areas of contiguous activation (Forman et al., 1995). Neuroanatomical locations of BOLD response differences surviving this threshold were identified with Talairach Daemon software (Lancaster et al., 2000), and manually confirmed with a standard neuroanatomy atlas (Talairach and Tournoux, 1988). The cluster thresholds were 640 μL (10 contiguous 4 mm³ voxels), 256 μL (4 contiguous 4 mm³ voxels), and 960 μL (15 contiguous 4 mm³ voxels), for the analyses focused on the prefrontal cortex, caudate nucleus, and whole brain, respectively.

The mean reaction times (RT) to no-go and go task trial types were measured, as were the overall accuracy scores specific to the no-go and go conditions. No-go accuracy was defined as the overall percentage of no-go trials that were correctly inhibited; thus, lower accuracy scores reflect commission (false alarm) errors. Go accuracy was defined as the overall percentage of go trials that were correctly selected, and thus lower accuracy scores reflect omission errors. In addition, signal detection measures d' and β were calculated, which, respectively, reflect the ability to distinguish go from no-go stimuli and response bias. Reaction times were compared between groups using analysis of variance (ANOVA), while accuracy and signal detection measures were analyzed with the Wilcoxon signed-rank test, due to the restricted range of these variables.

RESULTS

Analyses of accuracy and RT data were conducted on 17 of the 22 subjects, as behavioral data from 5 subjects (4 ALC, 1 CON) were lost due to mechanical failure of the hand-held response device. There were no statistically significant differences between the ALC and CON groups on RT to either go or no-go stimuli, accuracy scores on either trial type, or signal detection measures, d' and β (0.21 < p < 0.50). Response latencies, accuracy percentages, and signal detection measures are presented in Table 1.

To assess brain activation patterns during inhibitory control, independent samples t-tests compared BOLD response between groups on no-go relative with go task conditions. Based on ROI analyses, ALC individuals (n = 13) showed more no-go response (i.e., more BOLD activation during no-go trials relative to go trials) than CON subjects (n = 9) in prefrontal regions (e.g., right middle frontal gyrus, left superior frontal gyrus), but less no-go response in the right caudate nucleus. Whole-brain...
analyses revealed an area of the right parietal lobe, including the inferior parietal lobule, where ALC subjects showed more activation than their peers, while regions of the temporal and occipital lobes showed greater activation in CON participants (e.g., areas in the right cuneus and middle occipital gyrus). See Tables 2 and 3 and Fig. 2 for a summary of between-group BOLD response differences.

To further explore the nature of the results described above, 1-sample t-tests were conducted on the ALC and CON groups separately (see Fig. 3). These results suggest that the ROI-based analyses were driven by the following patterns during trials requiring response inhibition: ALC activation in the left prefrontal cortex, CON deactivation (i.e., less response during the task condition vs baseline fixation) in the right prefrontal cortex, and CON activation in subcortical regions. The more posterior temporal and occipital cortex CON > ALC activations revealed by whole brain analysis were driven largely by ALC deactivation in posterior cortical regions. Both groups showed task-related activation in bilateral medial frontal and cingulate cortical regions. In summary, the single-sample follow-up analyses suggest that the basis of the between-group differences on the no-go versus go task conditions (i.e., the group by condition interaction) varies by brain region. In summary, the overall pattern of BOLD response indicates that the observed frontal–striatal activation differences stem from the ALC group showing higher levels of BOLD response in the prefrontal cortex, and lower levels in the right caudate nucleus during trials that require response inhibition, compared with the response pattern of demographically similar nonexposed youth.

### Evaluation of Age Effects on BOLD Response Patterns

Because cognitive control abilities are expected to develop and consolidate as children mature, the influence of participant age on BOLD response is of interest to this study. Three post hoc regression analyses were conducted to explore the effects of patient age on between-group BOLD response comparisons. Individual average mean BOLD response values were extracted from the anatomical regions that emerged as significantly different between groups upon ROI analysis. Results regressing the mean nogo–go BOLD response on age were nonsignificant for the left superior frontal cluster, right middle frontal cluster, and right caudate cluster (0.20 < p’s < 0.91).

### Evaluation of FAS Diagnosis on BOLD Response Patterns

Neuropsychological evaluation of heavy cases of prenatal alcohol exposure suggest that similar behavioral teratogenic effects may occur irrespective of FAS diagnosis (cf. Mattson et al., 1997); however, this claim has not yet been evaluated with brain functional activation patterns. Analysis of variance was used to examine regional BOLD response across 3 participant groupings: CON (n = 9), ALC subjects with n = 6, and ALC subjects without (n = 7) a diagnosis of FAS. As expected, based on the original ROI results, omnibus effects were significant.

### Table 2. Region of Interest Analyses: Areas of Significant BOLD Response Differences Between ALC and CON on No-Go Condition Relative to Go Condition (n = 22, p < 0.05, corrected)

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Direction</th>
<th>Talairach coordinates</th>
<th>Cohen's d* (effect size r)</th>
<th>Brodmann's areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>R middle frontal gyrus</td>
<td>ALC &gt; CON</td>
<td>42 27 36</td>
<td>5.91 (0.95)</td>
<td>9</td>
</tr>
<tr>
<td>L superior, medial, and middle frontal gyri</td>
<td>ALC &gt; CON</td>
<td>−18 35 −12</td>
<td>7.56 (0.97)</td>
<td>11</td>
</tr>
<tr>
<td>R caudate nucleus and R lateral ventricle</td>
<td>CON &gt; ALC</td>
<td>6 −5 20</td>
<td>5.50 (0.94)</td>
<td></td>
</tr>
</tbody>
</table>

*Talairach coordinates and effect size calculations correspond to between-group maximum signal intensity difference within each cluster; coordinates are presented in LPI order (−x = left, −y = posterior, −z = inferior).

### Table 3. Whole Brain Analyses: Areas of Significant BOLD Response Differences Between ALC and CON on No-Go Condition Relative to Go Condition (n = 22, p < 0.05, corrected)

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Direction</th>
<th>Talairach coordinates</th>
<th>Cohen's d* (effect size r)</th>
<th>Brodmann's areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>R middle frontal gyrus</td>
<td>ALC &gt; CON</td>
<td>46 27 36</td>
<td>1.57 (0.62)</td>
<td>9</td>
</tr>
<tr>
<td>L superior, medial, and middle frontal gyri</td>
<td>ALC &gt; CON</td>
<td>−14 47 −12</td>
<td>1.26 (0.53)</td>
<td>11</td>
</tr>
<tr>
<td>R inferior parietal lobe and R supramarginal gyrus</td>
<td>ALC &gt; CON</td>
<td>54 −61 40</td>
<td>1.22 (0.52)</td>
<td>39, 40</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>ALC &gt; CON</td>
<td>−70 −57 0</td>
<td>1.57 (0.62)</td>
<td>21</td>
</tr>
<tr>
<td>R cuneus and middle occipital gyrus</td>
<td>CON &gt; ALC</td>
<td>18 −93 20</td>
<td>1.69 (0.64)</td>
<td>18, 19</td>
</tr>
<tr>
<td>R inferior and middle occipital gyri</td>
<td>CON &gt; ALC</td>
<td>46 −81 −4</td>
<td>1.38 (0.57)</td>
<td>18, 19</td>
</tr>
</tbody>
</table>

*Talairach coordinates and effect size calculations correspond to between-group maximum signal intensity difference within each cluster; coordinates are presented in LPI order (−x = left, −y = posterior, −z = inferior).
Bringing the 3 participant groupings for the regions revealed by ROI-based analyses for the motion main effect, but that the amount of applied correction did not differ by group \( F(1, 20) = 1.29, p = 0.27 \), nor was the motion×group interaction statistically significant \( F(5, 16) = 1.72, p = 0.14 \), indicating that the pattern of motion adjustment did not differ by group. See Table 1 for mean motion adjustment values by group.

Next, task-associated motion was estimated by correlating each of the bulk 6 motion parameters with the task reference vector (i.e., baseline, go, or no-go condition) for each time point measured during EPI acquisition. The mean correlation values were \(-0.01, -0.01, -0.02, -0.06, -0.02, -0.09\) for the CON group and those for the ALC group were \(-0.08, -0.07, -0.08, -0.05, -0.09, -0.03\) for motion correction related to roll, pitch, yaw, superior-to-inferior, left-to-right, and posterior-to-anterior axis displacements. Between-group analyses on these task-correlated motion estimates were conducted via nonparametric Spearman’s rank–order correlation. The relationship between group and left-to-right motion correction was significant \((\rho = 0.44; p = 0.04)\), indicating that the degree of task-associated left-to-right displacement varied by group. For the remaining motion parameters, no group differences were found \((0.06 < p's < 0.58)\).

Between-group analyses were rerun after removing 1 ALC subject, who was discrepant in degree of motion adjustment. The revised groups showed no statistical differences on task-correlated motion estimates, and results from this reanalysis were very similar to those from the original analyses, with 9 of 10 of the clusters reported in Table 3 being replicated to their original coordinates. One cluster, spanning the left fusiform gyrus and extending into the left cerebellum, was not replicated upon reanalysis, and an additional cluster of ALC>CON activation was identified in the right middle frontal gyrus. Region-of-interest–based analyses were replicated identically.

In summary, the results of these a priori analyses suggest that between-group BOLD response findings were not significantly influenced by gross motion artifact or task-correlated motion. Caution should be exercised, however, in interpreting the group difference localized to the left fusiform gyrus, as it was not replicated upon re-analysis.

Evaluation of Total Brain Volume

Lastly, the potential confound of volumetric brain differences between groups was considered. The high-resolution anatomical image of each participant was processed with the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain software library’s (FSL) brain extraction and automated segmentation tools (Smith, 2002; Zhang et al., 2001), and whole-brain voxel counts were conducted using AFNI’s 3dROIstats function (Cox, 1996; Cox and Hyde, 1997). A post hoc between-group comparison of total brain volume...
indicated that brain size did not differ between alcohol-exposed and comparison subjects \( F(1, 20) = 0.256, p = 0.62 \). This analysis provides some indication that the BOLD response patterns observed in this study were not unduly driven by between-group differences in brain size.

**DISCUSSION**

The main result of this investigation is that, despite equivalent task performance, FASD individuals showed increased BOLD response in the prefrontal cortex and decreased BOLD response in the caudate nucleus during trials that require the inhibition of action, compared with their typically developing peers. Thus, this result is consistent with our hypothesis that prenatal alcohol exposure may be associated with altered frontal–striatal activation patterns during response inhibition. More specifically, FASD individuals showed increased activation in regions of the right middle frontal gyrus and left middle, medial, and superior frontal gyri and decreased activation in the right caudate nucleus when comparing the difference between the no-go and go trials of the ALC and CON groups. If one assumes that increased activation is a consequence of appropriating greater cognitive resources to process the task at hand, one possible conclusion is that FASD subjects, relative to healthy comparison subjects, allocate more cortical effort to inhibit action. The greater prefrontal activation observed in individuals with prenatal alcohol exposure may indicate increased recruitment of these regions to mitigate decreased frontal–striatal network efficiency induced by alcohol teratogenesis. Over the course of typical development from childhood to adulthood, it appears that the prefrontal cortical activation associated with inhibitory control becomes more focused (Casey et al., 1997b; Tamm et al., 2002). Thus, increased activation of individuals with prenatal alcohol exposure may reflect an immature pattern of prefrontal cortical engagement. Future studies focused on functional connectivity would be useful in extending the present study’s results by more directly exploring the possibility that frontal–striatal network abnormalities underlie response inhibition deficits in FASD.

Interestingly, a within-group analysis of the no-go portion of the task indicated that while the ALC group increased activation in some of the regions that showed between-group differences (e.g., left frontal gyri),

![Fig. 3. Results from single sample task component t-tests \( z = 0.05 \), corrected overlaid on group anatomical brain image average for go relative to baseline condition, and no-go relative to baseline condition for CON and ALC groups. Colored areas indicate activation on task component of interest, as noted in key. Sagittal view (bottom left) depicts the extent of axial montage coverage.](image-url)
large-scale deactivation was still evident, especially in posterior midline regions. Decreased BOLD responses during task conditions are thought to be reflective of decreases in neuronal activation (Shmuel et al., 2006; Stefanovic et al., 2004), and so these results suggest that the ALC individuals were largely decreasing neuronal activity from baseline during task performance. This raises the possibility that spontaneous neural activity levels may differ between the groups. It is also possible that the decreased levels of ALC BOLD response in temporal and occipital cortices may reflect between-group differences on aspects of visual perception and object recognition.

To our knowledge, this is the first fMRI investigation of response inhibition in the FASD population. Thus, there is no extant literature examining the effects of prenatal alcohol exposure on BOLD response during inhibitory control with which to compare our data. However, our findings show concordance with several investigations of response inhibition in individuals with ADHD, a diagnosis that is associated with FASD (Bhatara et al., 2006). Consistent with our results, 2 previous fMRI studies using go/no-go response inhibition tasks observed frontal–striatal BOLD response abnormalities in children with ADHD (Durston et al., 2003; Vaidya et al., 1998). More specifically, both studies described activation patterns in the same direction as the present study, with ADHD children showing decreased striatal activation, and increased frontal region activation, compared with healthy peers. These findings from the ADHD literature converge with volumetric MRI data that correlate structural abnormalities in the prefrontal cortex and caudate nucleus with response inhibition performance deficits in individuals with ADHD (Casey et al., 1997a). However, there is some variability of results within the current literature, and other response inhibition studies of the ADHD population report findings that are divergent with those observed in the present FASD study, including hypofrontality of BOLD response (Rubia et al., 1999, 2005; Tamm et al., 2004). Variability among results of existing ADHD studies likely stems from myriad factors, including differences across studies in the medication status and age range of the participants (see Bush et al., 2005).

Previous MR studies have revealed morphometric alterations in brains of individuals with FASD, in comparison with typically developing individuals. In addition to an overall reduction in brain size, certain brain regions such as the corpus callosum, basal ganglia, and cerebellum appear to be especially vulnerable to the effects of alcohol teratogenesis (see Riley et al., 2004). Analyses of cortical shape have suggested that anterior and orbital frontal regions show changes in the form of reduced surface extent, with relative sparing of the dorsal aspects of the frontal lobe (Sowell et al., 2002). In addition, more posterior lobar abnormalities were indicated by a narrowing of inferior parietal and perisylvian regions. Along with these cortical shape findings, the results of the current study provide convergent evidence that alcohol teratogenesis produces disruptions to both the structure and function of specific brain regions. In particular, the frontal shape anomalies are interesting to consider, given the putative association of the orbitofrontal cortex with response inhibition. It may be that individuals with prenatal alcohol exposure hyperactivate prefrontal cortical regions when engaging inhibitory control to offset the effects of structural damage to orbitofrontal regions. Although such a relationship is merely speculative at this point, the prospect that the functional activation patterns observed in individuals with FASD may relate to regional structural anomalies is intriguing and warrants further investigation in future studies of this population. Although the finding that total brain volume did not differ between groups in this study is surprising, this discrepancy is potentially explained by sample differences, given that the alcohol-exposed participants in the present study were higher functioning, as measured by IQ estimates, than previously reported samples of structural MR studies.

Inconsistent with our hypothesis of increased commission error rate in the ALC group, between-group task performance was statistically equivalent for both trial types. The ALC group did perform more poorly than controls (76 vs 81% no-go accuracy), and so it is possible that with larger group sizes, response inhibition performance differences may emerge. Consideration of level of task difficulty, subject engagement, and behavioral performance equivalence is especially important in studies of pediatric clinical populations, as between-group performance differences can complicate interpretation of fMRI data (cf. Bookheimer and Sowell, 2005). A relatively easy go/no-go task was purposefully chosen for this initial response inhibition study to facilitate interpretation, but future work using a parametric task design would be useful in characterizing FASD BOLD response in the face of increasing inhibitory demands.

**Study Limitations**

Owing to the small sample size (n = 22) and large age range (8–18) of the individuals included in these analyses, these data should be considered a preliminary indication of brain response associated with inhibitory control following prenatal alcohol exposure. The large age range poses a limitation in interpreting these data, as developmental studies indicate that response inhibition continues to mature into adolescence (cf. Luna and Sweeney, 2004; Williams et al., 1999); thus, we likely sampled a variable range of response inhibition ability. However, we attempted to mitigate this limitation by using age as a matching variable, and by ensuring that the number of younger subjects (<12 years) was similar across groups (2 ALC subjects, 3 CON subjects). Additionally, the results of post hoc regression analyses do not suggest a significant age effect on BOLD response within this sample.
A further limitation to the current study is that psychoactive medication status differed between groups. Although, ideally, participants would be tested medication free, given the high rates of psychiatric symptoms commonly experienced by children with heavy prenatal alcohol exposure, we did not believe ALC subjects would tolerate the scanning procedure without routine medication. Exclusion of potential ALC subjects with psychiatric medication prescriptions is an alternative approach to address this issue but was not considered optimal in the interest of maximizing the generalizability of the study results to the FASD population at large.

Summary

Results from functional neuroimaging studies such as this one may support clinical efforts indirectly by providing an in vivo account of cognitive dysfunction in the FASD population. Further studies are needed to replicate the present study’s finding of altered frontal–striatal activation patterns in FASD. In particular, correlation of BOLD activation data with neurobehavioral task performance is indicated to help determine the relevance of the observed BOLD response differences to everyday functioning of individuals with FASD.

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REFERENCES


