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Effect of Predictive Cuing on Response Inhibition in Children with Heavy Prenatal Alcohol Exposure

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Abstract

Background—Heavy prenatal exposure to alcohol leads to widespread cognitive deficits, including problems with attention and response inhibition. This study examined blood oxygen level-dependent (BOLD) response in children with and without histories of heavy prenatal alcohol exposure during a task of response inhibition consisting of cued and non-cued trials.

Methods—Children and adolescents (ages 8-18y) with (AE=20) and without (CON=15) histories of heavy prenatal exposure to alcohol underwent functional magnetic resonance imaging (fMRI) while performing a go/no-go task. Unbeknownst to subjects, a predictive cue preceded the no-go stimulus in 87% of trials.

Results—Groups were matched on demographic variables and did not differ on most measures of task performance. However, following cued stimuli, the AE group demonstrated a lower hit rate to go stimuli and more conservative response bias than the CON group. Alcohol-exposed participants demonstrated more activation during no-go trials (inhibition) relative to go trials in the left precuneus, cingulate gyrus, anterior cingulate, and right medial frontal gyrus. During cue-dependent response inhibition, the AE group demonstrated less activation in the left pre-central and post-central gyrus compared to the CON group.

Conclusion—Consistent with previous studies of response inhibition, alcohol-exposed children demonstrated greater frontal and parietal activation when attempting to inhibit prepotent responses than controls, despite similar rates of commission errors. This study further demonstrated that alcohol-exposed children had impaired behavioral performance on cued trials and demonstrated less activation in pre-central and post-central gyri relative to controls on these trials. This investigation provides evidence of impaired behavioral and neural processing of sequential information in FASD, which can help improve inhibition in typical populations.

Keywords

Fetal alcohol spectrum disorders (FASD); fetal alcohol syndrome (FAS); response inhibition; cognitive control; functional neuroimaging

Introduction

Fetal alcohol syndrome (FAS) results from heavy prenatal alcohol exposure (AE) and is defined by three diagnostic criteria: central nervous system dysfunction, pre- and postnatal growth deficiencies, and specific craniofacial features (short palpebral fissures, indistinct philtrum, and thin vermillion) (Hoyme et al., 2005; Jones and Smith, 1973; Stratton et al., 1996). Neurobehavioral impairments and neuroanatomical abnormalities observed in FAS are often observed in children with confirmed histories of AE who do not meet all diagnostic criteria required for FAS (Mattson et al., 2011; Mattson and Riley, 1998; Vaurio et al., 2010). The non-diagnostic umbrella term fetal alcohol spectrum disorders (FASD) has been adopted to capture the range of consequences of prenatal exposure to alcohol (Bertrand et al., 2004). The prevalence of FASD is estimated to be as high as 2-5% of the population in the US and some Western European countries (May et al., 2009) and has been identified in all racial and ethnic groups (Abel, 1995). Children with AE can suffer from cognitive deficits in overall intellectual functioning and on indices of learning, memory, attention, and executive functioning (Mattson et al., 2011). Additionally, they may demonstrate behavioral problems including hyperactivity and impulsivity (Vaurio et al., 2010), or show changes in brain structure (Lebel et al., 2011; Norman et al., 2009).

Both human and animal model studies have indicated that response inhibition, the ability to suppress irrelevant stimuli to facilitate efficient, goal-directed behavior, appears to be particularly sensitive to the teratogenic effects of alcohol (Barron and Riley, 1990; Connor et al., 2000; Gallo and Weinberg, 1982; Mattson et al., 1999; McGee et al., 2008; Riley et al., 1979; Streissguth et al., 1986; Streissguth et al., 1984). Rodent models indicate that AE leads to behavioral disinhibition, as evidenced by poorer performance on measures of reversal learning and passive avoidance (Barron and Riley, 1990; Gallo and Weinberg, 1982; Riley et al., 1979). Human studies employing a variety of methodologies have indicated similar deficits in inhibitory control. On behavioral rating scales, both parents and teachers rate children with AE as having clinically significant levels of inhibitory problems (e.g., not thinking before acting, leaving seat in school, and interrupting others) (McGee et al., 2008; Rasmussen et al., 2006; Rasmussen et al., 2007). On neuropsychological measures of inhibition such as the Stroop Test (Strauss et al., 2006), individuals with AE make more errors than non-exposed peers, and these deficits cannot be wholly accounted for by deficits in lower order skills or intelligence (Connor et al., 2000; Mattson et al., 1999). On continuous performance tasks, children with AE display increased rates of commission and omission errors, as well as slower reaction times and a lower ratio of correct to incorrect responses (Streissguth et al., 1986; Streissguth et al., 1984). However, some studies have failed to find a relationship between AE and inhibitory deficits on neuropsychological measures, especially when exposure levels were low (Boyd et al., 1991; Fried et al., 1992).

As a result of the reported neuropsychological deficits following AE, recent research has begun to explore response inhibition through physiological techniques. These studies have suggested that even when behavioral performance on measures of response inhibition is similar between children with AE and non-exposed controls, subjects with AE have different patterns of electrophysiological (Burden et al., 2009; Burden et al., 2011) and hemodynamic (Fryer et al., 2007) brain response when inhibiting prepotent responses. In event-related potential (ERP) studies of response selection and inhibition, children with AE show similar accuracy rates and response times as non-exposed peers, but demonstrate different patterns of neural activation for P2, P3, and N2 ERP components. Compared to unaffected children, neural activation of individuals with AE is consistent with less efficient processing of visual information, lack of early discrimination between go and no-go stimuli, less efficient

cognitive effort during inhibition, and diminished frontal activation on inhibitory trials (Burden et al., 2009; Burden et al., 2011).

In a functional magnetic resonance imaging (fMRI) study examining response inhibition with comparable behavioral performance in children with and without AE, children with AE showed increased blood oxygen level dependent (BOLD) response in the prefrontal cortex and decreased BOLD response in the caudate nucleus during trials requiring inhibition compared to non-exposed peers (Fryer et al., 2007). This study suggested that children with AE allocated more cortical effort during inhibition, possibly indicating inefficiency of implicated cortical regions due to the teratogenic effects of alcohol. In conjunction, these studies suggest that even when performance on measures of response inhibition appears to be unaffected in children with AE, the teratogenic effects of alcohol may still affect underlying neural mechanisms of inhibition.

Many real world situations of inhibition are preceded by cues that indicate inhibition of an action will be required in the near future. For example, a red light in traffic signals the need to stop, but is usually preceded by a yellow light that serves as an advance warning. For children, a teacher standing at the front of the classroom may signal the need to stop talking and prepare for a lesson. Successful inhibition in such situations requires the ability to resist immediate prepotent responses as well as recognizing cues signaling the likelihood of impending inhibition (Leland et al., 2008). Cued go/no-go paradigms present stimuli that predict the need to respond or inhibit before no-go stimuli appear, improving both reaction time and inhibitory performance in typical populations (Arce et al., 2006; Leland et al., 2008; Miller et al., 1991). Research in healthy populations has implicated the role of the parietal cortex in processing predictive information (Adam et al., 2003; Schmid et al., 2001). Given the response inhibition deficits associated with AE, it is important to study potential ways to improve inhibitory abilities for affected children.

The present study investigated whether predictive cuing on a go/no-go paradigm improved inhibitory performance or affected BOLD activation in children with AE as compared to non-exposed peers. Based on previous findings from this task in alcohol-exposed individuals (Fryer et al., 2007), we hypothesized that on trials requiring inhibition, children with AE would show greater activation in frontal areas and lesser activation in subcortical areas compared to typically developing controls. Additionally, given findings of cue-dependent inhibition in healthy and patient adult populations (Arce et al., 2006; Leland et al., 2008), we hypothesized that on cued, as compared to non-cued, inhibitory trials, alcohol-exposed subjects would show greater activation in frontal and temporal regions than controls, reflecting greater cognitive effort to utilize cues.

Materials and Methods

Subjects

Study subjects included children and adolescents between 8 and 18 years of age with histories of AE (the AE group; $n=20$) and typically developing peers (the CON group; $n=15$). Children were recruited as part of a larger ongoing study of the teratogenic effects of alcohol. Children with AE were recruited through several mechanisms, including professional referral or self-referral and are considered to have heavy prenatal alcohol exposure. Mothers of children in the AE group consumed at least four drinks per occasion at least once per week or fourteen drinks per week during pregnancy. History of AE was determined through multiple sources, including review of available medical, social service, and adoption agency records, and maternal report, when available. Direct maternal report was generally unavailable, as many children with heavy prenatal exposure to alcohol no longer reside with their biological families ($AE=17$). Children in the AE group were

evaluated by a dysmorphologist with expertise in alcohol teratogenesis. FAS diagnoses were based on physical measurements (height or weight <10 percentile), craniofacial structure analysis (presence of at least 2 of the following: short palpebral fissures, smooth philtrum, thin vermilion), evidence of deficient brain growth or abnormal morphogenesis (at least 1 of the following: structural brain abnormalities, head circumference <10th percentile), and alcohol exposure history (Hoyme et al., 2005; Jones et al., 2006; Mattson et al., 2010). The AE group included children who met criteria for FAS ($n=8$) and children with confirmed heavy prenatal alcohol exposure but who did not have all physical features required for an FAS diagnosis ($n=12$).

Non-exposed participants were recruited from the community via advertising at various agencies and child-related venues. The majority of children in the control group in our sample reside with their biological mothers so screening for exposure to alcohol or other teratogens was determined through direct maternal report. Mothers of these children reported little (i.e., <1oz alcoholic drink per day prior to pregnancy recognition), if any, alcohol use during pregnancy. These procedures are in agreement with normative standards for retrospective confirmation of maternal alcohol use within the field of clinical behavioral teratology (Mattson et al., 2010).

Study eligibility criteria for both groups required that subjects be between the ages of 8 and 18, right-handed, and native English speakers. Exclusionary criteria for both groups included head trauma, contraindication for MRI scanning (e.g., metallic implants in the body), claustrophobia, or serious medical conditions (e.g., epilepsy). Additionally, CON subjects were excluded if they had a diagnosis of psychiatric illness or were taking psychoactive medications. Eleven of the 20 children in the AE group were on prescribed psychoactive medications at the time of scanning. Medication type included ADHD medication (atomoxetine, methylphenidate, dextroamphetamine, clonidine), antidepressants (bupropion, sertraline, trazodone), and antipsychotics (risperidone, aripiprazole, quetiapine). A subset of these subjects was included in a previous study of response inhibition, though the effect of cue was not examined (Fryer et al., 2007).

Prior to participation, 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. Subjects were provided with financial incentive for participation.

Task Description

During the event-related go/no-go task (Leland et al., 2008), participants viewed serial presentations of blue shapes on a computer screen, all in the same fixed sequence: 18 blocks of 10 trials each with baseline rest periods of 0-40 s between blocks. Intertrial intervals served as fixation periods and were pseudo-randomly interspersed between blocks. Trial 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 milliseconds (ms) with an inter-trial interval of 1,500 ms. Subjects were instructed to press a button each time the large circle, small circle, or large square appeared (go stimuli), and *not* to press when the small square was shown (no-go stimulus). Unbeknownst to subjects, the large square served as a predictive cue for no-go trials (see **Figure 1**). The large square appeared in 24% of trials, and was followed by the small square 87% of the time.

Prior to the scan session, verbal and pictorial instructions were used to train participants on the go/no-go task. Participants practiced the task on a laptop computer to ensure comprehension of task instructions. After the scan session, participants were asked if they thought the shapes were presented in a sequential pattern, and if so, what this pattern was.

Questions were scored qualitatively as follows: Did not recognize any pattern, recognized a pattern but could not describe it, recognized a pattern and reported it partially correctly (e.g., small shapes and large shapes alternate), or recognized the pattern correctly (i.e., large blue square predicts small blue square).

Neuroimaging Procedures

Brain images were acquired on a GE 3-Tesla magnet using an 8-channel head coil. After a localizer scan to ensure optimal head placement, a high-resolution anatomical scan [fast spoiled gradient sequence, TR=8,000 ms, TE=3.1 ms, flip angle=12°, 256 × 192 matrix, 1 mm slice thickness, 24 cm field of view, acquisition time=7 min 24 seconds] was collected for coregistration with the functional protocol. Subjects viewed a movie during anatomical image acquisition.

BOLD-weighted functional imaging was collected axially with the following echo planar sequence parameters: TR=3,000 ms, TE=32 ms, flip angle=90°, in-plane resolution=3.43 mm × 3.43 mm, 4 mm slice thickness × 30 slices for whole brain coverage, 24 cm field of view, 128 repetitions, and acquisition time=6 min 24 seconds. Task stimuli were displayed using locally developed software, and inversely projected onto a screen at the subjects' feet. Behavioral responses were recorded via a fiber-optic response system (Current Design, Pittsburgh, PA). The go/no-go task was collected as part of a larger neuroimaging battery, for which the total scan time was approximately 60 minutes.

Data Analysis

Data analysis was completed using similar procedures to those in our previous study (Fryer et al., 2007). Analysts blind to group classification processed fMRI data using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996; Cox and Hyde, 1997). To correct for small movements over time, image repetitions were registered to a selected base volume using the AFNI 3D volume registration program (Cox and Jesmanowicz, 1999) to estimate three rotational (roll, pitch, yaw) and three displacement (superior-to-inferior, left-to-right, posterior-to-anterior) parameters for each participant. Then, time series data were visually inspected for gross movement artifacts; a dataset was excluded if more than 15% of repetitions were judged by two independent raters to have visually discernable movement. Data from 3 AE and 7 CON subjects not described in this sample were thus excluded due to excessive movement. To quantify the amount of movement for each remaining subject, the absolute values of the motion parameters were averaged and compared to group means. In the remaining sample, the average motion parameters did not exceed two standard deviations from the population mean for any subject in any direction. No significant between-group differences were found in the number of TRs censored ($F(1,33)=0.352$, $p=.56$).

Time series data were deconvolved with a task reference vector representing the task design while accounting for hemodynamic delays and covarying for the degree of motion correction applied (Bandettini et al., 1993). Fixation periods were incorporated into AFNI's baseline. This yielded fit coefficients for each voxel representing BOLD response to each condition (go, unpredicted no-go, predicted no-go). Functional data were transformed into standard space (Talairach and Tournoux, 1988), resampled to 4mm³ voxels, and a spatial smoothing Gaussian filter (full-width half maximum=5mm) was applied.

Group-level analyses were performed on whole-brain fMRI data using independent sample *t*-tests with an unpooled error estimate. We examined BOLD response differences between no-go trials (small square) and go trials (all other shapes), and differences between cued no-go trials (small square following a large square) and non-cued no-go trials (small square

following a large or small circle). Only significant between-group activations that consisted of at least 15 contiguous voxels ($p < .01$, clusters $> 960 \mu\text{L}$) were interpreted to control for Type I error (Forman et al., 1995). Neuroanatomical locations of BOLD response differences surpassing this intensity and extent threshold were identified with Talairach Daemon software (Lancaster et al., 2000) and manually confirmed with a standard neuroanatomical atlas (Talairach and Tournoux, 1988). Individual BOLD response contrast fit coefficients, averaged across all voxels in the cluster, were extracted from the anatomical regions that emerged as significantly different between groups and imported to SPSS so relationships with demographic and behavioral variables could be examined.

Mean reaction times (RT) and accuracy were recorded for both go and nogo stimuli. No-go accuracy was defined as the overall percentage of no-go trials that were correctly inhibited; thus, lower accuracy scores reflect disinhibition errors (i.e., false alarms or commission errors). Go accuracy was defined as the overall percentage of go trials that were correctly selected, thus lower accuracy scores reflect omission errors (i.e., misses). In addition, signal detection measures d' and β were calculated, which reflect the ability to distinguish go from no-go stimuli, and response bias, respectively. An alpha level of $p < .05$ was used to determine statistical significance. Alpha levels of $p < .10$ were considered to be marginally significant. Behavioral data were compared between groups using analysis of variance (ANOVA) and pattern recognition measures were analyzed using chi-square in SPSS.

Results

Demographics

Groups were matched on age, sex, race/ethnicity, and socioeconomic status (SES) as measured by the Hollingshead index (Hollingshead, 1975). Full scale IQ (FSIQ) scores were available from previous testing with the Wechsler Intelligence Scale for Children, III (Wechsler, 1991) or the Wechsler Intelligence Scale for Children, IV (Wechsler, 2004). As expected, children in the AE group had significantly lower FSIQ scores than children in the CON group [$F(1,32)=8.108$, $p=.008$]. Demographic data are presented in **Table 1**.

Task Performance

Behavioral data from 6 subjects (4 AE, 2 CON) were lost due to mechanical failure so data were available for 29 of the 35 subjects. For non-cued trials (small square preceded by a large circle or small circle), AE and CON groups did not differ on RT, accuracy, or signal detection measures for either go or no-go stimuli (all $p > .10$). On cued trials (small square preceded by a large square), the AE group performed significantly worse on go-trial accuracy ($F(1,27)=4.94$, $p=0.035$) and had a more conservative response bias (β) [$F(1,27)=5.84$, $p=0.023$]. No group differences were found for either condition on behavioral measures of inhibition (see **Table 2**). Given that all subjects were required to meet an accuracy cutoff of 80%, there were too few error trials to permit robust modeling of the hemodynamic response to errors of commission or omission, so error trials were not modeled separately. In addition, because behavioral data were missing for six subjects, both correct and incorrect responses for the remaining subjects were included in the model used to examine BOLD response.

Pattern Recognition

Sixteen of the 35 subjects (AE=8) reported that they thought the stimuli were presented in a sequential pattern. Nine of these 16 subjects (AE=4) had no guess as to what the pattern was, five subjects (AE=3) reported a partially correct pattern, and two subjects (AE=1) reported the pattern correctly (i.e., big square predicts little square). There were no significant group differences on measures of pattern recognition ($0.424 < \chi^2 < 0.740$).

fMRI Response

To assess brain activation patterns during inhibitory control, independent sample *t*-tests compared BOLD response between groups on no-go relative to go task conditions. Because both correct and incorrect responses were included in the model for BOLD response, results should be interpreted as neural activation associated with attempts to inhibit a prepotent response rather than successful inhibition. Alcohol-exposed individuals showed more no-go response (i.e., more BOLD activation during no-go trials relative to go trials) than control subjects in the left precuneus and cingulate gyrus (Brodmann's areas 7 and 31) [$F(1,33)=6.02$, $p=.02$] and anterior cingulate and right medial frontal gyrus (Brodmann's areas 32 and 10) [$F(1,33)=10.48$, $p<.01$] (see **Figure 2**). To assess the effect of cues, BOLD response was compared between groups on cued relative to non-cued no-go trials. During cue-dependent response inhibition (as compared to non-cue dependent inhibition), the AE group demonstrated less activation in the left pre-central and post-central gyri (Brodmann's areas 3 and 4) [$F(1,33)=7.55$, $p=.01$] compared to the CON group (see **Table 3** and **Figure 3**).

To further explore the nature of the aforementioned results, single sample *t*-tests were conducted on the AE and CON groups separately (see **Figure 4**). On trials requiring inhibition, both groups showed frontal and parietal activation though the control group showed a negative BOLD signal change and the alcohol-exposed group demonstrated a positive BOLD signal change. The AE group also showed activation in more widespread areas, especially in the left hemisphere. Additionally, only the alcohol-exposed group showed activation in subcortical regions (i.e., caudate and thalamus). On cued inhibitory trials, compared to non-cued inhibitory trials, both groups demonstrated parietal activity, but only the alcohol-exposed group showed frontal activation and only the control group showed activation in the pre- and post-central gyrus.

Effect of Behavioral Performance

To ensure that the neural effects of error-related processing did not confound results, only subjects with a hit rate of greater than 80% across trials were included in the analysis. One AE subject not described in this sample was excluded due to inadequate behavioral performance. Because behavioral data were unavailable for 6 subjects, BOLD response was examined in the remaining 29 subjects. Between-group differences in BOLD activation remained significant for the two clusters associated with inhibition ($.001 < p < .005$) and the cluster associated with cued inhibition ($p=.01$)

Groups differed on IQ, but research has suggested that covarying for IQ in populations with developmental disabilities is inappropriate both statistically and theoretically, given potential confounds including population representativeness and non-linearity with other neuropsychological domains (Dennis et al., 2009). However, given the significant performance differences between groups on cued trials, go-trial accuracy and response bias were investigated as potential covariates for BOLD response during this contrast. Pearson correlations between behavioral data and mean activation in the pre-central and post-central gyri revealed no significant correlations across the sample ($r<.16$, $p>.42$) or within the AE ($r<.13$, $p>.63$) or CON ($r<.10$, $p>.75$) groups separately.

Effect of participant head motion

Because AE is associated with hyperactivity, potential differences in head motion during the scan session were examined. Groups did not differ on any measures of task-correlated motion, though children in the AE group did have significantly more posterior/anterior bulk motion ($p=.03$). However, this motion was not significantly correlated with BOLD response on go/no-go or cued/non-cued contrasts ($.18 < r < .30$, $09 < p < .31$). Because the relationship

between motion and BOLD response approached significance ($r=.30$), areas with between-group differences in BOLD activation were examined with posterior/anterior bulk motion as a potential covariate. Group differences remained significant for the two clusters associated with inhibition ($.006 < p < .05$) and the cluster associated with cue-dependent inhibition ($p=.04$).

Effect of age

Because cognitive abilities are expected to develop throughout adolescence, the influence of participant age on behavioral and BOLD response is of interest in this study. To explore the possible effect of age on behavioral data, post hoc correlations were run between age and each behavioral variable. No significant correlations were found for any behavioral measures on either cued or non-cued trials across groups (cued: $.002 < r < .08$, $.69 < p < .99$; non-cued: $.05 < r < .11$, $.15 < p < .79$) or within the AE (cued: $.01 < r < .28$, $.27 < p < .97$; non-cued: $.09 < r < .17$, $.51 < p < .73$) or CON (cued: $.03 < r < .25$, $.35 < p < .91$; non-cued: $.08 < r < .22$, $.36 < p < .91$) groups separately. Post hoc correlation analyses were also conducted to explore the possible effects of age on BOLD response. No significant correlations emerged between age and extracted cluster means on the go/no-go or cued/non-cued contrast across groups ($.04 < r < .15$, $.38 < p < .82$) or within the AE ($.11 < r < .29$, $.14 < p < .65$) or CON ($.01 < r < .15$, $.59 < p < .98$) groups separately.

Effect of FAS diagnosis

Neuropsychological evidence has shown that children with heavy prenatal exposure to alcohol show similar deficits regardless of FAS diagnosis (Vaurio et al., 2010). However, this finding is less established in neuroimaging literature, so post-hoc analyses were used to examine the effect of FAS diagnosis on inhibition-related brain activation. ANOVA was used to examine regional BOLD response for extracted cluster means across three participant groups: CON ($n=15$), AE subjects with a diagnosis of FAS ($n=8$), and AE subjects without a diagnosis of FAS ($n=12$). As expected, omnibus effects were significant among the three participant groups for the regions revealed by whole-brain analyses ($0.01 < p < 0.04$). No significant differences in BOLD activation emerged between alcohol-exposed children with and without a FAS diagnosis ($0.22 < p < 0.54$), suggesting FAS status did not have an effect on between-group differences in BOLD activation.

Discussion

On a task of cued response inhibition, children with AE displayed different patterns of neural activation than non-exposed controls. The alcohol-exposed group showed *greater* activation on trials signaling the need to inhibit a response in the left precuneus, cingulate gyrus, anterior cingulate, and right middle frontal gyrus despite equivalent inhibitory behavioral performance across trials. However, alcohol-exposed children showed *less* activation on trials when cues signaled the need to inhibit a response in the left pre- and post-central gyrus compared to non-exposed peers and showed lower go accuracy and a more conservative response bias on cued trials. Despite well-established deficits in response inhibition in children with FASD, children in the AE group had similar rates of inhibitory errors to those in the CON group. This was likely due to the simplified nature of this go/no-go task for use in the fMRI environment, and may suggest that inhibitory deficits in FASD are most devastating under more complex demands. However, despite the similar performance on inhibitory trials, the AE group displayed different patterns of neural activation during attempts to inhibit compared to non-exposed peers, suggesting that neural activity underlying inhibition may be compromised even on simple inhibitory tasks.

Greater frontal and parietal activation associated with attempts to inhibit a prepotent response in alcohol-exposed subjects is consistent with our hypothesis and with previous functional neuroimaging studies of inhibition, working memory, and attention in alcohol-affected children and adolescents (Fryer et al., 2007; Malisza et al., 2005; O'Hare et al., 2009; Sowell et al., 2007; Spadoni et al., 2009). Furthermore, activation of frontal-parietal networks in both the AE and CON groups is consistent with previous fMRI studies of response inhibition (Simmonds et al., 2008). More specifically, greater activation of prefrontal regions during inhibitory control is consistent with a previous study examining go/no-go performance in alcohol-affected children (Fryer et al., 2007). Previous studies suggest that greater activation in frontal and parietal lobes during inhibition, as seen in alcohol-affected children, reflects neural compensation for inefficient processing by frontal-parietal networks (Fryer et al., 2007). Alternatively, greater frontal-parietal activation may reflect an immature pattern of inhibitory processing as inhibitory networks become more efficient and localized across development (Casey et al., 1997; Durston et al., 2006; Tamm et al., 2002). These results also converge with the literature on structural abnormalities in AE, including volumetric reductions, increased gray matter, and decreased white matter in frontal and parietal lobes (Archibald et al., 2001; Sowell et al., 2001; Sowell et al., 2002), increased cortical thickness in the parietal lobe (Sowell et al., 2008), and lower white matter integrity of tracts innervating the frontal and parietal lobes, such as the superior longitudinal fasciculus (Fryer et al., 2009; Lebel et al., 2008). Taken together, this evidence suggests that frontal-parietal abnormalities may contribute to deficits in response inhibition previously identified in children with AE (Connor et al., 2000; Mattson et al., 1999; Streissguth et al., 1994).

The current study did not replicate previous reports of reduced subcortical activation in the AE group, compared to the CON group, during trials requiring inhibition (Fryer et al., 2007). In fact, single-group activation maps in the current study suggest that only the AE group showed an increase in BOLD signal in subcortical regions during attempts to inhibit. These contrasting findings may be due to the larger sample size ($n=35$) and more conservative alpha rate ($<.01$) of the current study, as well as the fact that the current study used a whole-brain rather than ROI analysis. Given the well-documented structural abnormalities in subcortical structures following AE (Archibald et al., 2001; Mattson et al., 1996; Roussotte et al., 2011), additional research is needed to clarify the relationship between subcortical structures and inhibitory deficits in this population.

On cued inhibitory trials, as compared to non-cued inhibitory trials, children with AE showed less activation in the left pre- and post-central gyrus than controls. Additionally, children with AE had a lower hit rate (i.e., lower go trial accuracy) and a more conservative response bias than non-exposed subjects on cued trials, suggesting they did not benefit from the implicit cue. However, groups were matched on rates of commission errors and measures of pattern recognition, with only one subject in each group correctly identifying the large square as a predictive cue for the no-go stimulus. To the best of our knowledge, no functional imaging studies have examined the effect of implicit cuing on inhibition in developmental populations, though studies examining implicit sequence learning on serial reaction time (SRT) tasks have implicated the involvement of the left pre- and post-central gyri (Hazeltine et al., 1997; Thomas et al., 2004). Adults are more likely to show activation in these areas than children (Thomas et al., 2004) and enhanced recruitment of the motor cortex during SRT tasks is associated with greater time spent learning an implicit sequence in typical populations (Karni et al., 1995; Karni et al., 1998). The lesser activation demonstrated by AE subjects in the pre- and post-central gyrus on cued trials, as well as the lower hit rate and more conservative response bias, may suggest the implicit sequence was not utilized to the same extent to predict response inhibition and could reflect underlying deficits in non-verbal learning. Children with AE have previously been shown to have

problems with non-verbal learning, with some studies suggesting that non-verbal learning may be more impaired than verbal learning in this population (Mattson and Roebuck, 2002). The failure of alcohol-exposed children to benefit from the implicit cues may account for the reduced activation in this region.

Despite these novel findings, several limitations should be considered. First, because a predictive cue preceded no-go stimuli 87% of the time, behavioral measures and BOLD response data were averaged over fewer trials for non-cued than cued no-go stimuli for each participant. The relatively low frequency of non-cued no-go stimuli may have decreased statistical power to detect effects on these trials. Another possible limitation of this study is the broad age range (8-18 years) of participants. Response inhibition abilities continue to mature into adolescence, thus we likely sampled a variable range of inhibitory abilities. However, groups were matched on age and post-hoc analyses indicated that age was not significantly related to behavioral performance or BOLD activation, either across or within groups. Another possible limitation of this study is that 11 of the 20 children in the alcohol-exposed group were on routinely prescribed psychoactive medications at the time of scanning. Psychotropic medications have been found to affect BOLD response in various populations, but such effects vary by task, medication type, and participant diagnosis (e.g., Brown and Eyler, 2006; Marquand et al., 2012). Though excluding children on medication from this study would have greatly reduced our sample size, additional research is needed to examine the short- and long-term effects of psychoactive medications on BOLD response in alcohol-affected populations. Lastly, the majority of children in the AE group in this study do not reside with their biological parents ($n=17$), whereas only one subject in the CON group did not reside with a biological parent. Children who are not raised by a biological parent may be more likely to experience multiple home placements and/or reside in less stable and nurturing homes, experiences which have been found to relate to adverse life outcomes in individuals with AE (Streissguth et al., 2004). Though the relationship between cognitive skills and home placement has yet to be examined, it is possible that our results were affected by home placement status.

This is the first study to investigate the role of implicit cuing in response inhibition in AE. This study supports previous research on abnormal neural activation underlying inhibition in alcohol-affected children and adds that implicit cuing may not improve inhibitory abilities in children with AE in the same way such cues benefit non-affected children. Future research is needed to better understand behavioral performance on measures of implicit cuing and sequence learning in alcohol-affected children. Because children with AE do not seem to benefit from predictive cuing, further investigations are needed to understand other strategies that may be used by affected individuals to compensate for deficits in response inhibition.

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Figure 1.
Go/No-Go Task Instructions and Stimuli

Figure 2.

Group differences in BOLD response on inhibitory trials for alcohol-exposed (AE) and non-exposed control (CON) subjects. On inhibitory trials, AE subjects showed more BOLD response than CON subjects in the left precuneus/cingulate gyrus (posterior cluster) and anterior cingulate/right medial frontal gyrus (anterior cluster).

Figure 3.

Group differences in BOLD response on cued inhibitory trials for alcohol-exposed (AE) and non-exposed control (CON) subjects. On cue-dependent inhibitory trials, CON subjects showed more BOLD response than AE subjects in the left precentral/postcentral gyrus.

Figure 4. Single group activation maps for inhibitory (top) and cue-dependent inhibitory (bottom) contrasts for alcohol-exposed (AE; left) and non-exposed (CON; right) subjects. Red and yellow clusters indicate a positive change in BOLD activation, while blue clusters indicate a negative change in BOLD activation.

Figure 5.

Difference in BOLD response (i.e., beta weights) in clusters with significant between-group differences for the inhibitory (no-go – go; L precuneus/cingulate gyrus and anterior cingulate/R medial frontal gyrus) and cue-dependent inhibitory (cued no-go – uncued no-go; L precentral/postcentral gyrus) contrasts. Data are presented as mean $\pm$ standard error of the mean for alcohol-exposed (AE) and non-exposed control (CON) subject groups.

Table 1

Demographic and motion characteristics for alcohol-exposed (AE) and non-exposed control (CON) subject groups

	AE	CON	<i>P</i>
<i>N</i>	20	15	
Age (y) (M ± SD)	14.77 ± 2.90	13.63 ± 2.64	NS [*]
Sex [n (%) female]	6 (30)	8 (53)	NS
Race [n (%) Caucasian]	13 (65)	11 (73)	NS
SES (M ± SD)	45.92 ± 10.48	42.97 ± 17.61	NS
FSIQ (M ± SD)	90.90 ± 9.15	102.50 ± 14.63	0.01
Motion-roll ^a (M ± SD)	0.08 ± 0.07	0.09 ± 0.06	NS
Motion- pitch (M ± SD)	0.21 ± 0.15	0.16 ± 0.12	NS
Motion- yaw (M ± SD)	0.08 ± 0.06	0.13 ± 0.10	NS
Motion- superior/inferior (M ± SD)	0.23 ± 0.20	0.17 ± 0.08	NS
Motion- left/right (M ± SD)	0.06 ± 0.04	0.08 ± 0.07	NS
Motion- posterior/anterior (M ± SD)	0.11 ± 0.06	0.07 ± 0.03	0.03

^{*} NS, nonsignificant (*p* > .10)

^a Bulk motion values refer to the mean amount of motion correction applied along a given axis, in millimeters

Table 2

Behavioral data for cued and non-cued go/no-go trials for alcohol-exposed (AE) and non-exposed control (CON) subject groups. Cued trials were defined as those following a large square; non-cued trials were defined as those following a small square, large circle, or small circle.

Cued trials	AE (M ± SD)	CON (M ± SD)	P
Hits	55.00 ± 5.01	58.15 ± 1.07	0.04
False Alarms	8.19 ± 4.45	8.77 ± 6.09	NS *
Correct Inhibition	22.81 ± 4.45	22.23 ± 6.09	NS
D-Prime	2.44 ± 0.89	2.83 ± 0.78	NS
Response Bias ()	0.38 ± 0.31	0.16 ± 0.09	0.02
Go mean reaction time (ms)	738.53 ± 138.08	674.43 ± 143.82	NS
Go accuracy (%)	0.93 ± 0.08	0.99 ± 0.02	0.04
No-go mean reaction time (ms)	620.63 ± 138.97	589.07 ± 131.24	NS
No-go accuracy (%)	0.74 ± 0.14	0.72 ± 0.20	NS

Non-Cued Trials	AE (M ± SD)	CON (M ± MD)	P
Hits	59.06 ± 6.88	62.46 ± 1.71	NS
False Alarms	6.25 ± 3.40	7.00 ± 5.89	NS
Correct Inhibition	19.75 ± 3.40	19.00 ± 5.89	NS
D-Prime	2.46 ± 0.89	2.84 ± 1.00	NS
Response Bias ()	0.43 ± 0.36	0.28 ± 0.23	NS
Go mean reaction time (ms)	731.18 ± 144.91	668.08 ± 120.74	NS
Go accuracy (%)	0.92 ± 0.11	0.98 ± 0.03	NS
No-go mean reaction time (ms)	620.85 ± 161.07	570.87 ± 140.59	NS
No-go accuracy (%)	0.76 ± 0.13	0.73 ± 0.23	NS

* NS, nonsignificant ($p > 0.10$)

Table 3

Areas of significant BOLD response differences between alcohol-exposed (AE) and non-exposed control (CON) groups ($n=35$, $p<.01$, corrected)

Anatomical region	Effect Size Cohen's <i>d</i>	Brodmann Area	Volume (μl)	Talairach Coordinates ^a		
				X	Y	Z
No-Go – Go Activation (AE > CON)						
L precuneus and cingulate gyrus	0.82	7, 31	2993	1	52	31
Anterior cingulate and R medial frontal gyrus	1.08	32, 10	1857	−15	−44	−9
Cued No-Go – Non-cued No-Go Activation (CON > AE)						
L pre-central and post-central gyrus	0.73	3, 4	1296	30	25	64
L <i>left</i>						
R <i>right</i>						

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