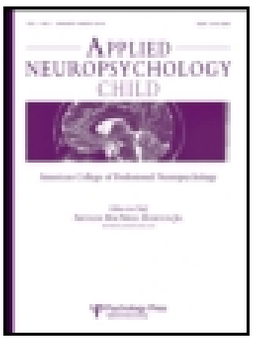

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Effects of prenatal substance exposure on neurocognitive correlates of inhibitory control success and failure

Leslie E. Roos, MS[a,b], Kathryn G. Beauchamp, MS[a], Katherine C. Pears, PhD[b], Philip A. Fisher, PhD[a], Elliot T. Berkman, PhD[a], and Deborah Capaldi, PhD[b]

[a]Department of Psychology, University of Oregon, Eugene, Oregon; [b]Oregon Social Learning Center, Eugene, Oregon

ABSTRACT

Adolescents with prenatal substance (drug and alcohol) exposure exhibit inhibitory control (IC) deficits and aberrations in associated neural function. Nearly all research to date examines exposure to individual substances, and a minimal amount is known about the effects of heterogeneous exposure—which is more representative of population exposure levels. Using functional magnetic resonance imaging (fMRI), we investigated IC (Go/NoGo) in heterogeneously exposed ($n = 7$) vs. control ($n = 7$) at-risk adolescents (ages 13–17). The fMRI results indicated multiple IC processing differences consistent with a more immature developmental profile for exposed adolescents (Exposed > Nonexposed: NoGo > Go: right ventrolateral prefrontal cortex, right cuneus, and left inferior parietal lobe; NoGo > false alarm: occipital lobe; Go > false alarm: right anterior prefrontal cortex). Simple effects suggest exposed adolescents exhibited exaggerated correct trial but decreased incorrect trial activation. Results provide initial evidence that prenatal exposure across substances creates similar patterns of atypical brain activation to IC success and failure.

KEYWORDS

Error processing; fMRI; inhibitory control; prenatal exposure

Understanding the effects of prenatal substance exposure on developmental outcomes is a key public health issue. Greater than 4.4% of all newborns are exposed monthly to one or more substances during pregnancy, with exposure to alcohol and marijuana occurring at rates as high as 10 to 11% (NAIARC, 2012; Wendell, 2013). Recent changes in the use of illicit substances and conceptualized legal status of drugs such as marijuana further highlight the importance of understanding longitudinal effects of prenatal exposure (Mohler-Kuo, Lee, & Wechsler, 2003).

Previous literature on the neurocognitive consequences of prenatal exposure has aimed to quantify the effects of *specific* substances such as alcohol, cocaine, methamphetamine, or marijuana. This approach has been useful for highlighting the impacts of a wide variety substances on brain development and for noting the particularly impairing qualities of certain substances, such as alcohol (Noland et al., 2003). However, a "specific substance" focus is limited by the substantial variability in timing and dosage of exposure and the common experience of polysubstance exposure in prenatally exposed samples (Havens, Simmons, Shannon, & Hansen, 2009; NAIARC, 2012). The extensive overlap of neural systems affected across substances (i.e., alcohol, marijuana, cocaine, methamphetamine, and opiates) provides further rationale for using naturalistic samples that may have heterogeneous substance exposure experiences. Candidate neural system aberrations across substances include dysregulation of key dopaminergic and serotonergic neurotransmitter systems, atypical neuronal growth patterns, and vasoconstriction, which can result in reduced fetal blood flow or fetal hypoxia (Derauf, Kekatpure, Neyzi, Lester, & Kosofsky, 2009; Minnes, Lang, & Singer, 2011). Research on ecologically valid samples with heterogeneous exposure experiences is thus needed as a complement to the extant specific substance literature in order to understand the risk imparted for a substantial proportion of adolescents with polysubstance prenatal exposure.

Inhibitory control, defined as the ability to inhibit prepotent or ongoing motor responses, is an important skill to understand in prenatally exposed samples because of the disinhibited and impulsive behaviors characteristic of this population (Ackerman, Riggins, & Black, 2010; Day, Leech, & Goldschmidt, 2011; O'Connell et al., 2009). Prior research in prenatally exposed samples has frequently (Carmody, Bennett, & Lewis, 2011; Derauf et al., 2012; Mattson, Goodman,

CONTACT Leslie E. Roos, MS lroos.uoregon@gmail.com Department of Psychology, 1227 University of Oregon, Eugene, OR 97402.
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Caine, Delis, & Riley, 1999; A. M. Smith, Fried, Hogan, & Cameron, 2004), but not consistently (Fryer et al., 2007) found exposure-related deficits in inhibitory control across substances. We expected that a sample of adolescents with heterogeneous exposure would exhibit inhibitory control impairment because impairment is frequently reported across substances of exposure. Furthermore, the mechanisms through which substances are theorized to impair brain development (e.g., dopaminergic pathways) are documented to be particularly pronounced in frontal brain regions, key to complex cognitive functions such as inhibitory control (Derauf et al., 2009).

Examining brain activity during inhibitory control tasks may provide additional clarity about the neurocognitive processes underlying inconsistent behavioral results. These techniques, such as functional magnetic resonance imaging (fMRI), allow researchers to compare how brain activity supporting a given cognitive skill (e.g., successful inhibitory control), compares to brain activity related to cognitive skill failure (e.g., unsuccessful inhibitory control) or another skill domain (e.g., sustained attention as indexed by successful "Go" trials). Through this comparison, inferences can be made about differential cognitive processing in a given at-risk group, which may be related to prenatal exposure.

In the present research, we investigated exposure-related activation for both successful and unsuccessful inhibitory control trials, given the frequent behavioral deficits associated with prenatal exposure. This was assessed in the Go/NoGo behavioral task, in which participants are asked to respond as quickly as possible to Go stimuli (~75% of trials) and to inhibit a response to NoGo stimuli (~25% of trials; Carmody et al., 2011). Withholding a response on NoGo trials is considered successful inhibitory control, while responding on a NoGo trial is considered a "false alarm" failure of inhibitory control. To further probe inhibitory control related brain activation, we identified three contrasts of interest comparing: (a) the difference between successful inhibitory control (NoGo trials) versus sustained attention-only (Go trials), (b) the difference between successful inhibitory control (NoGo trials) versus unsuccessful inhibitory control (false alarm trials), and (3) the difference between sustained attention-only (Go trials) versus unsuccessful inhibitory control (false alarm trials).

Previous fMRI research in prenatally exposed samples has primarily focused on brain activation differences in the first contrast [successful inhibitory control (NoGo vs. Go)]. These studies have fairly consistently shown increased BOLD activation in prenatally exposed (vs. nonexposed) samples in frontal regions (i.e., middle, superior, and inferior frontal gyri, and orbitofrontal gyri) and have had inconsistent findings of either more or less activity in posterior areas such as parietal lobes, cerebellum, caudate nucleus, occipital lobes, or cuneus during NoGo versus Go trials (Fryer et al., 2007; Sheinkopf et al., 2009; A. M. Smith et al., 2004).

Previous research has not examined brain activation associated with inhibitory control failures in prenatally exposed samples, but we suggest that examining this error-related brain activity may be important for understanding inhibitory control impairment. Brain regions associated with inhibitory control develop during early adolescence and individuals with inhibitory control exposure are commonly found to exhibit more frequent inhibitory control failures during this time (Braet et al., 2009; Bridgett & Mayes, 2011; Coles, Platzman, Lynch, & Freides, 2002). Examining patterns of activation associated with false alarm trials may illuminate the extent to which prenatal exposure contributes to differences in error-related processes.

Previous fMRI research of samples with prenatal exposure is limited by a lack of information about the association between brain activation and behavioral performance. Despite reporting effects of prenatal exposure on both performance and functional activation indices, most fMRI studies do not examine if these are statistically associated (Li et al., 2008). Even in research that does not find between group differences in behavior, it may be valuable to examine whether individual differences in brain activation (associated with exposure) predict performance heterogeneity given the link between inhibitory control performance deficits and negative behavioral outcomes (such as substance abuse).

Goals of the study

In this study, we examined a group of adolescents ($N = 7$) with prenatal exposure to a range of substances including alcohol, marijuana, methamphetamines, cocaine, and opiates. Notably, adolescents in the prenatally exposed group had heterogeneous exposure experiences with some adolescents having exposure to only one substance (e.g., alcohol or opiates) while others experienced poly substance exposure (e.g., alcohol and marijuana). All of the participants were considered at risk given that their fathers were recruited as children from higher-risk neighborhoods for the Oregon Youth Study (OYS). Furthermore, the participants' fathers exhibited relatively high rates of delinquency and substance use during adolescence and adulthood (Capaldi, Chamberlain, & Patterson, 1997; Capaldi, Stoolmiller,

Kim, & Yoerger, 2009). The participants (offspring of the OYS men) are now part of the Three Generational Study (3GS) of the intergenerational transmission of substance use and other risky behaviors (Capaldi, Pears, Patterson, & Owen, 2003. The control adolescents ($N = 7$) were also drawn from this sample and are therefore a particularly appropriate control group due to their comparable history of familial risk.

To understand better the impacts of heterogeneous prenatal exposure to substances on neurocognitive functioning, behavioral indices and neuroimaging correlates of inhibitory control skills were examined. We drew from previous literature on prenatally exposed (vs. nonexposed) samples and developmental (vs. adult) samples to establish hypotheses based on the assumption that adolescents who experienced exposure would have brain activity consistent with a more developmentally immature profile. Previous investigators have suggested that prenatal exposure may contribute to delayed (or stunted) development of cortical regions so individuals with prenatal exposure exhibit brain activation associated with younger developmental stages (Fryer et al., 2007; A. M. Smith et al., 2004). We also examined if the groups differed in behavior problems or cognitive tests of intelligence to ensure that these factors did not account for group differences in neural activation.

Specifically, in the first contrast of interest (NoGo vs. Go), it was hypothesized that the exposed (vs. nonexposed) group would have increased activation in frontal regions for NoGo vs. Go trials. This is based on consistent findings of increased prefrontal activation associated with prenatal exposure, which is believed to reflect reduced specificity in resource recruitment. Group differences were also expected in brain activation associated with NoGo trials in posterior regions, such as the cuneus and occipital lobes, but which group would display increased activation was not predicted given the aforementioned inconsistences in the literature. For the second contrast of interest (NoGo vs. false alarm), it was expected that the nonexposed group would have greater activation than the exposed group to false alarm trials in medial (e.g., insula, caudate) and occipital regions, given previous findings of increased activation in these regions associated with more mature samples (Braet et al., 2009). For the final contrast of interest (Go vs. false alarm), it was expected that the prenatally exposed group would exhibit increased frontal region recruitment for the correct Go trials and decreased frontal activation for false alarm trials (reflecting a less mature activation profile). In order to better understand processes driving the results, we planned to conduct visual inspection of simple effects for each region with significant between group differences in activation.

If activation differences were found in frontal areas, it was hypothesized that they would be associated with reduced inhibitory control performance, as they may be indicative of atypical functioning of frontal executive regions, which are important for inhibitory control. Atypical activation in posterior regions was not hypothesized to be related to performance, because activation of these areas may reflect atypical early-stage processing that would be less likely to predict inhibitory control deficits.

Method

Participants

Participants were recruited from the ongoing Three Generational Study (3GS). This study examines the adolescent offspring of the original Oregon Youth Study (OYS) participants. The OYS is a 30-year longitudinal study focused on the development of antisocial behavior and substance use in boys (Capaldi, Chamberlain, Fetrow, & Wilson, 1997). The original OYS men were recruited as children from schools in at-risk neighborhoods, as determined by areas with higher rates of juvenile crime. Within these schools, all 4th grade boys (Generation 2; G2) and their parents (Generation 1; G1) were eligible to participate, and a sample of 206 families was recruited. The current study focuses on the third generation of participants (Generation 3; G3), who are the biological adolescent offspring of the G2 men (Capaldi et al., 2003). For practical considerations, only the first two adolescents of each G2 man and any given mother were eligible to participate in the 3GS study.

For the fMRI component of the study, adolescents between the ages of 13 and 17 from October 2011 to June 2012 who had been prenatally exposed to substances by maternal report (described as follows) and adolescents from the same sample who were matched in age and gender to the exposed adolescents were initially recruited to participate. Twenty-nine families were originally interested in participating, including 16 exposed and 13 nonexposed adolescents. Of these participants, 15 (eight exposed, seven nonexposed) were not able to participate due to anxiety about fMRI procedures, physical contraindications for scanner participation, moving out of town, or failure to respond to repeated efforts to schedule an appointment. Our final sample with complete fMRI data included seven adolescents with prenatal substance exposure and seven adolescents without exposure (see the Materials section for additional information on substances of exposure).

Once eligible fMRI participants were identified, they completed a phone screening to ensure they were right-hand dominant, fluent in English, had no history of head injury or epilepsy, and no MRI contraindications, and were not currently taking psychotropic medication (other than stimulant medication). Those adolescents on stimulant medication were asked to take a 24-hour medication wash-out period prior to testing.

Demographic data were collected by a maternal report questionnaire and included child age and gender. The mean age of participants was 14.14 years ($SD = .95$). The sample was 64.3% male. All participants were of Caucasian race/ethnicity. As shown in Table 1, mothers had completed an average of about 11 years of schooling. The exposed and nonexposed groups did not significantly differ on education, or on age or gender (as assessed using two-tailed independent sample *t*-tests and Fisher's exact-probability test). Descriptive statistics and prenatal exposure history are shown in Table 1.

Procedure

Eligible participants attended a 1.5 hour-long session at the Lewis Center for Neuroimaging (LCNI) on the University of Oregon campus. Participants and their caregivers provided assent and informed consent (respectively) prior to the scanning session. Participants also practiced the Go/NoGo task on a laptop computer to ensure that they understood task instructions and procedure. After completing one practice block of the task, participants were situated in the scanner by a professional MR technician, and the scanning session began. During the session, event-related fMRI data were recorded while adolescents completed two runs of the Go/NoGo task. Additional neuroimaging data including diffusion tensor imaging and resting state functional connectivity were collected but are not presented here.

Measures

Prenatal exposure

Each child's prenatal exposure was determined by maternal self-report on a retrospective pregnancy health questionnaire, administered when their adolescents were 2–3 years of age. This included frequency of alcohol and drug use during pregnancy on a 9-point Likert scale from 'never' to "2–3 times a day or more." The questionnaire asked about a variety of substances used during pregnancy including tobacco, marijuana, hallucinogens, inhalants, alcohol, opiates, uppers (including methamphetamine), downers, and tranquilizers. Adolescents were considered prenatally exposed if their mother reported using any alcohol or illicit drugs more than "never" at any point during the pregnancy. Mothers of prenatally exposed adolescents reported alcohol ($n = 4$, 57.1%), opiate ($n = 4$, 57.1%), marijuana ($n = 3$, 42.9%), upper ($n = 1$, 11.1%), and downer ($n = 1$, 11.1%) usage, which resulted in four adolescents (57.1%) with polysubstance exposure. Adolescents with prenatal exposure may have also experienced prenatal exposure to cigarettes ($n = 1$), but adolescents were excluded from the control group if they experienced prenatal cigarette exposure. Frequency of substance use varied across substances and participants within the sample ranging from one drink or toke "once or occasionally" to weekly opiate use.

Intelligence and behavior problem assessment

Intelligence testing was conducted for 13 of 14 participants at the previous 3GS study assessment [child age 11–12; $M(SD) = 11.46(.52)$] with the *Weschler Intelligence Scale for Children – Fourth Edition* (WISC-IV; Wechsler, 2003). From this testing, verbal and nonverbal intelligence quotients were obtained for participants. The group average scaled score for the

Table 1. Demographics and between group statistical comparisons.

Variable	Nonexposed	Exposed	Statistical comparison
Age (years) [M(SD)]	15.00 (1.49)	14.44 (.99)	$t(12) = .82$, $p > 0.05$
Sex (% Male)	42.9%	85.7%	Fisher's exact test, $p > .05$
Race/Ethnicity (% Caucasian)	100%	100%	ns
Maternal education, Last grade completed [M(SD)]	10.57 (1.13)	11.17 (1.60)	$t(11) = -.98$, $p > .05$
Go trial accuracy (%)	98.8 (1.3)	97.9 (1.8)	$t(12) = 1.07$, $p > .05$
Go trial reaction time, ms [M(SD)]	406.91 (39.12)	422.82 (46.78)	$t(12) = -1.17$, $p > .05$
NoGo trial accuracy (%)	59.92 (20.78)	44.05 (15.08)	$t(12) = 1.64$, $p > .05$
False alarm trial reaction time [M(SD)]	357.66 (24.38)	400.24 (49.64)	$t(12) = -2.04$, $p > .05$
CBCL Internalizing Problems	53.71 (16.59)	42.17 (10.30)	$t(11) = 1.47$, $p > .05$
CBCL Externalizing Problems	52.29 (12.07)	36.83 (4.26)	$t(11) = 2.97$, $p < .05$
WISC-IV Vocabulary Score	10.14 (3.39)	10.00 (2.10)	$t(11) = .09$, $p > .05$
WISC-IV Block Design Score	8.43 (2.70)	9.50 (.55)	$t(11) = -.95$, $p > .05$
Single substance exposure			
Opiates (N)	–	3	
Polysubstance exposure			
Alcohol, marijuana (N)	–	2	
Alcohol, uppers, downers, marijuana (N)	–	1	
Alcohol, opiates (N)	–	1	

verbal IQ was 8.92 (2.02) and the nonverbal was 10.08 (2.75).

Behavior problems were assessed by maternal report on the Child Behavior Checklist externalizing and internalizing subscales. (Achenbach, 1991). Mothers were asked to base their ratings on child behavior during the past 6 months at child age 11–12. The CBCL Internalizing scale included items from three domains: withdrawal, somatic complaints, and anxiety/depression. The withdrawal domain includes problems related to a child's shyness, withdrawal, and inclination to be alone, and the somatic complaints domain includes child symptoms related to aches, fatigue, or stomach problems. Anxiety/depression items included child experiences of sadness, fear, perfectionism, and worry. The Externalizing scale included items related to aggressive symptoms (e.g., attention seeking, arguing, bragging, teasing, having a temper) and delinquent symptoms (e.g., lying, cheating, stealing; Achenbach, 1991). Across all participants, internalizing t-scores were 48.38 (14.76; range 33–76) and externalizing T-scores were 45.15 (12.02; range 30–73), which are similar scores to normative samples (Achenbach, 1991).

Go/NoGo task

A standard Go/NoGo task was used as described by Durston et al. (2002). Participants selectively responded to frequent target (Go) stimuli by pushing a button on a button box (75% of trials), while inhibiting the Go response to infrequent nontarget NoGo stimuli (25% of trials). The NoGo stimulus was a specific number (3), while Go stimuli included all other numbers (1, 2, 4). Participants were instructed to press the button as fast as possible for Go stimuli, while inhibiting a response for NoGo stimuli. During these trials, a single-digit black number was presented on a white background screen for 500 ms, which was followed by a 1000 ms response window. The interstimulus interval was variable ($M = 2375$ ms, range = 1750–3000 ms) to improve statistical efficiency for modeling the hemodynamic response for specific trial types. In order to account for the effects of motor response on brain activation, half of the adolescents in each group used their right hand when pressing the button, and the other half used their left. As determined by Pearson's correlations, the hand used was not significantly related to accuracy or reaction time ($p > .05$).

Participants completed two runs of the task, each with one block of 72 trials (75% Go trials and 25% NoGo trials). Each block had a different pseudorandom order and was preceded by a baseline rest period (30 s), which served as the baseline condition for contrasts with the experimental trial type conditions. During this rest period, adolescents were asked to look at a fixation point. Each run lasted approximately 5 min and 20 s for a total of 10 min and 40 s of scanning time for this task.

All aspects of the tasks including stimulus presentation, reaction time recording, and accuracy recording were completed using Presentation (Neurobehavioral Systems, Inc.). A digital projector/reverse screen display was used to present stimuli on a screen at the back of the MRI scanner. The participants viewed this screen via a mirror in the MRI scanner and responded on an MRI-compatible fiber-optic button response box.

fMRI data acquisition and preprocessing

A Siemens Allegra 3 Tesla head-only MRI scanner was used to acquire fMRI data scans from the entire brain at LCNI. A standard eight-channel birdcage coil was used to acquire all images. Earplugs and sound-attenuating headphones were worn by the adolescents, and padding was placed between the coil and earphones to minimize head movement.

Prior to the functional scans, a 46 s auto alignment scan was completed that allowed for subsequent acquisition independent of the head position. The two functional runs lasted approximately 5 min and 20 s each and involved an echo-planar 2D blood oxygen level-dependent (BOLD) sequence (TR = 2000 ms, TE = 30 ms, flip angle = 80°, FOV = 200 mm, 32 contiguous 4 mm thick interleaved slices, 64 × 64 matrix, spectral fat saturation, bandwidth = 2604 Hz). An amount of 160 whole brain volumes per functional run were acquired (total 320). After the participant completed all trials, a T1-weighted anatomical image with optimal grey-white matter contrast was acquired using a modified inversion magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE TR = 2500 ms, TE = 4.38 ms, TI = 1100 ms, flip angle = 8°, matrix size 256 × 192, FOV = 256 mm, 160 slices, 1 mm in-plane resolution, 1 mm thick) lasting 8 min. Head motion during the functional runs was partially corrected using prospective acquisition correction (PACE; Thesen, Heid, Mueller, & Schad, 2000), and motion of less than 1.5 mm was considered acceptable. Additional steps were taken to account for motion during preprocessing as described in the following section.

MRIConvert was used to convert the raw neuroimaging data to Neuroimaging Informatics Technology Initiative (NIfTI) data format (http://lcni.uoregon.edu/~jolinda/MRIConvert/). Additional preprocessing included removal of nonbrain tissue from images using FSL's Brain Extraction Tool (S. M. Smith, 2002) and realignment of the functional images, normalization of all images into Montreal Neurological Institute standard stereotactic space, and smoothing of all images with a

6 mm full width half maximum (FWHM) isotropic Gaussian kernel using Statistical Parametric Mapping (SPM) version 8 (http://www.fil.ion.ucl.ac.uk/spm/). Additional motion correction was performed on all neuroimaging data using motion parameters derived from PACE. Specifically, volumes related to motions "spikes" (i.e., a difference of > 1.5 mm between two sequential volumes) were statistically accounted for by adding regressors of no interest corresponding to these volumes. Across all subjects and all runs, 17 such volumes were identified. No included subject had more than six spikes.

Data analysis

Behavioral data

We calculated performance accuracy, reaction time, and all *t*-tests using SPSS v.19. All data satisfied assumptions of normality with no outliers (±3SD) on any behavioral performance indices.

fMRI data

All inferential fMRI analyses were completed in SPM8. We estimated event-related condition effects, according to the general linear model, using high pass filters (128 s), a canonical hemodynamic response function and first order auto-regressive error structure. Events modeled at the individual level included: correct Go trials, correct NoGo trials, incorrect Go trials, incorrect NoGo trials (i.e., false alarms), and rest (Implicit Baseline). The first comparison of interest (termed inhibitory control) refers to the NoGo > Go contrast. Other comparisons of interest include the NoGo > false alarm and Go > false alarm contrasts. For each comparison of interest, we created linear contrasts at the individual level that were then imported to the group-level for random effects analyses [between group (exposed $N = 7$, nonexposed $N = 7$)]. We also examined the NoGo versus Go contrast across the whole group ($N = 14$) to determine inhibitory control network activity across the entire sample. For all analyses, we used Analysis of Functional Neuroimages (AFNI) AlphaSim software (Cox, 1996) to apply a cluster-size correction for multiple comparisons. This software used Monte Carlo simulations to estimate the probability that a random field of noise will produce clusters of voxels of a range of sizes accounting for the size of the search space and estimated smoothness. The minimum cluster sizes necessary to yield family-wise false-positive rates of 5% with voxel-level thresholds of $p < .001$ were 24 voxels for the whole group analysis of the NoGo versus Go contrast, 21 voxels for the between group analysis of the NoGo versus Go contrast, 22 voxels for the between group analysis of the NoGo versus false alarm contrast, and 30 voxels for the between group analysis of the Go versus false alarm contrast.

To determine that the Go/NoGo task indeed elicited established patterns of inhibitory control, we first examined group-level contrasts of NoGo versus Go across all participants. Next, we examined our main research questions regarding the differences in neural activation between adolescents exposed to prenatal substances and a matched sample of adolescents not exposed to substances during NoGo, false alarm, and Go trials. To estimate the degree to which differences between prenatally exposed and nonexposed adolescents were meaningfully related to behavioral indices associated with exposure, we next extracted parameter estimates of blood oxygen level dependent (BOLD) activation from significant clusters and compared them to behavioral performance differences on the Go/NoGo task.

Results

Preliminary analyses

Covariates of child age, child gender, child race, and maternal education, intelligence (verbal and nonverbal), and behavior problems were examined to identify possible between group differences based on prenatal exposure. As indicated in Table 1, statistical tests (independent sample *t*-tests and Fisher's exact test) performed in SPSS v.19 indicated no significant differences between groups, with the exception of the externalizing behavior problems on the CBCL. As noted in Table 1, the nonexposed (versus exposed) adolescents exhibited higher levels of behavior problems, however, these problem T-scores were very close to population averages (population $M = 50$, $SD = 10$; nonexposed $M = 52.29$, $SD = 12.07$), and well below the clinical cut off (70). Because the externalizing behavior problems scores were not of clinical concern, we refrained from further analyses, particularly because the intelligence testing results were so similar.

Go/NoGo behavioral results

In order to test the hypothesis that prenatally exposed adolescents would have poorer inhibitory control performance on the Go/NoGo task than would nonexposed adolescents, independent sample two-tailed *t*-tests were conducted comparing the groups. There was no significant difference in NoGo trial percent accuracy between the groups, nor were there significant differences between group differences in incorrect NoGo trial (i.e., false alarm) reaction time, Go trial accuracy, or

Table 2. Functional brain activation statistical comparisons.

Group	Contrast	Anatomical region	x	y	z	t	z	k
Whole group	NoGo > Go	Middle temporal gyrus	51	−39	6	7.53	4.60	137
		R putamen/insula	30	24	0	4.96	3.65	136
		L putamen/insula	−36	18	0	4.06	3.21	44
		R inferior frontal gyrus	48	6	33	4.66	3.51	36
Between groups (Exposed > Nonexposed)	NoGo > Go	R ventrolateral prefrontal cortex	48	18	27	3.61	2.91	27
		R cuneus (occipital lobe)	6	−78	9	7.96	4.61	534
		L inferior parietal	−57	−51	27	6.83	4.28	71
	NoGo > false alarm	L cuneus (occipital lobe)	−18	−84	−9	5.11	3.66	43
		R fusiform gyrus/occipital lobe	15	−57	−12	4.03	3.14	25
		R cuneus/precuneus	18	−69	27	4.84	3.54	461
	Go > false alarm	R anterior prefrontal	24	45	18	4.56	3.41	57

Go trial reaction time. However, it is noteworthy that the nonexposed group tended to have better indices of task performance (reaction time and accuracy), and null results may be a consequence of limited statistical power and small sample size. See Table 1 for descriptive statistics and independent sample *t*-tests.

fMRI results

Defining the inhibitory control network

To confirm that participants completed the task as expected, we investigated the effect of inhibitory control relative to sustained attention only (NoGo > Go) across all participants ($N = 14$) because results from this contrast are well-established in the developmental fMRI literature (Durston et al., 2002). This analysis revealed patterns of activation in typical inhibitory control regions including the middle temporal gyrus, bilateral putamen/insula, and right inferior frontal gyrus (Table 2; Simmonds et al., 2007).

Between group functional activation differences

As shown in Table 2, multiple between group activation differences were found across the three contrasts of interests. Across all significant clusters from the between group analyses, the exposed group had significantly greater activation than the nonexposed group. Post hoc analyses examining between-group activation in each of the significant clusters were performed for each "active" condition (i.e., Go, NoGo, and false alarm) versus rest in order to elucidate the specific activation differences driving these interactions.

In the NoGo > Go contrast, the exposed group had significantly greater activation in the right ventrolateral prefrontal cortex, right cuneus, and left inferior parietal cortex (Table 2, Figure 1). Activation differences in the right ventrolateral prefrontal cortex appeared to be driven by a significant difference in activation in NoGo trials (vs. rest [independent sample *t*-test, $t(12) = -2.63$, $p < .05$], with exposed adolescents having exaggerated NoGo versus rest activation, compared to the

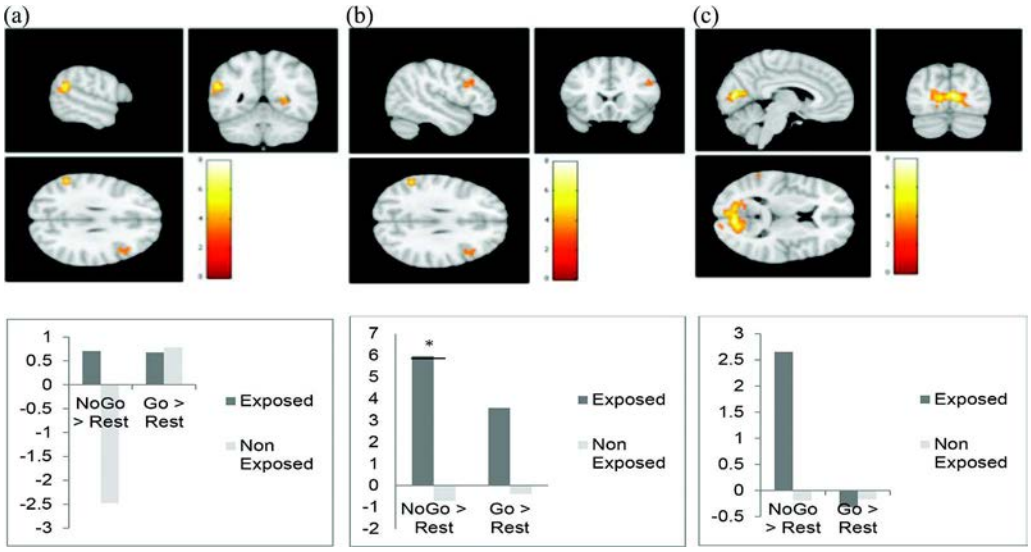

Figure 1. Significant clusters of functional activation for the NoGo > Go contrast in the left inferior parietal cortex (a; [−57 − 51 27]), right ventrolateral prefrontal cortex (VLPFC; b; [48 18 27]), and right cuneus (c; [6 − 78 9]). Parameter estimates from each cluster are provided for each component of the contrast (e.g., NoGo > rest, Go > rest) for each group to demonstrate patterns of activation driving the results (differences significant at level of $p < .05$ indicated by*).

nonexposed adolescents (Figure 1b). For the two other clusters with significant between group differences (i.e., right cuneus and left inferior parietal cortex), post-hoc *t*-tests revealed no significant differences in the individual simple effects contrasts versus rest (Figure 1c,a). Visual inspection, however, suggests that activation during NoGo trials may be driving the interaction. The exposed group demonstrated exaggerated activation in the right cuneus during NoGo versus rest, compared to the nonexposed group in which there was minimal activation change. In the left inferior parietal cortex, the exposed group exhibited slight activation in NoGo versus rest, while the nonexposed group exhibited substantial de-activation.

For the NoGo > false alarm contrast, the exposed group had significantly greater activation than the nonexposed group in the right fusiform gyrus, left cuneus and right cuneus/precuneus (Table 2, Figure 2). A visual examination of simple effects in the left cuneus revealed that the exposed group tended to have less deactivation (vs. rest) for NoGo, compared to false alarm trials, while the nonexposed group had more deactivation for NoGo compared to false alarm trials (Figure 2a). The nonexposed group had significantly greater deactivation for NoGo trials, compared to false alarm trials [paired sample *t*-test, $t(6) = 4.71$, $p < .01$], while the exposed group showed no difference between trial types. An examination of activation in both the right fusiform gyrus and right cuneus/precuneus revealed no significant simple effects driving the interaction, but the pattern of results suggested that the nonexposed group exhibited larger activation differences between trial types (greater activation during false alarm vs. NoGo trial), while there were minimal activation differences in the exposed group (Figure 2b, c).

Finally, in the Go > false alarm contrast, the exposed group had significantly greater activation than the nonexposed group in the right anterior prefrontal gyrus (Figure 3). There were no significant between or within group simple effect differences. However, based on a visual examination of results from the simple effects models, the exposed group exhibited relatively more activation for Go compared to false alarm trials, while the nonexposed group exhibited more activation for false alarm compared to Go trials.

Associations of neuroimaging findings with behavioral performance differences

A series of correlations were conducted to test if indices of brain activation were related to inhibitory control performance accuracy. Specifically, whether an individual's NoGo accuracy was related to their average parameter estimate of functional activation across all voxels in each of the seven significant clusters from the between-group analyses of the three contrasts of interest (Table 2) was examined. Bivariate Pearson's correlations indicated that NoGo performance was marginally (but not significantly) related to certain areas of between-group activation in each contrast. Specifically, in the NoGo > Go contrast, activation in right ventrolateral prefrontal cortex was marginally negatively related to NoGo trial accuracy ($r = -.50$, $p < .10$). In the

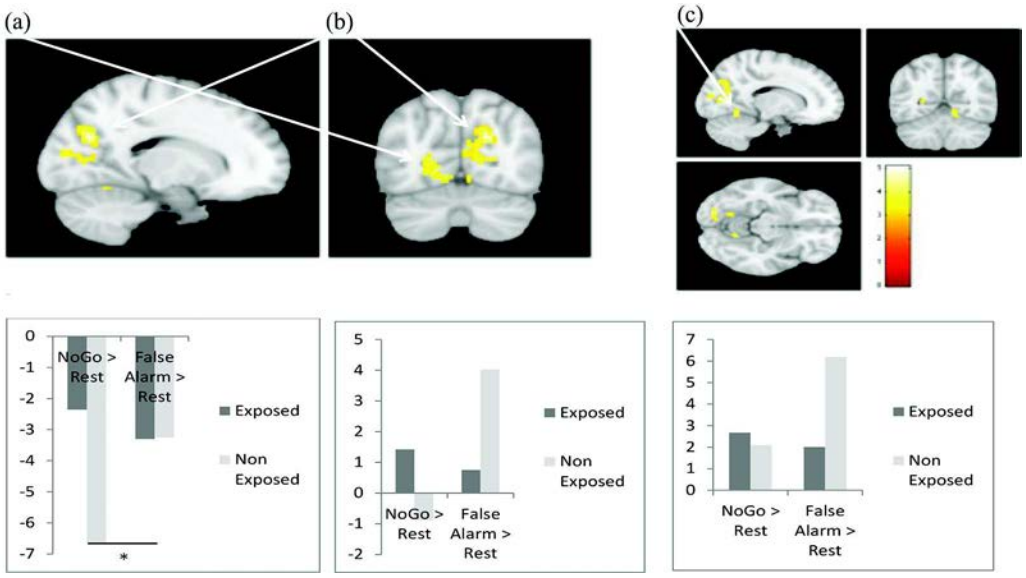

Figure 2. Significant clusters of functional activation for the NoGo > false alarm contrast in the left cuneus (a; [−18 −84 −9]), and right cuneus/precuneus (b; [18 −69 27]), and right fusiform gyrus (c; [15 −57 −12]. Parameter estimates from each cluster are provided for each component of the contrast (e.g., NoGo > rest, false alarm > rest) for each group to demonstrate patterns of activation driving the results (differences significant at level of $p < .05$ indicated by *).

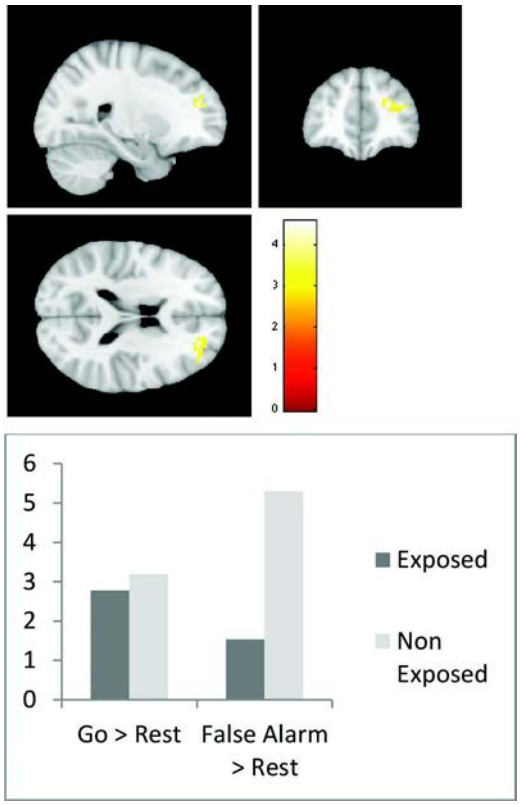

Figure 3. Significant cluster of functional activation for the Go > false alarm contrast in the anterior prefrontal/middle frontal cortex. Parameter estimates from this cluster are provided for each component of the contrast (e.g., Go > rest, false alarm > rest) for each group to demonstrate patterns of activation driving the results.

NoGo > false alarm contrast, activation in the left cuneus/middle occipital gyrus was marginally negatively related to NoGo trial accuracy ($r = -.52$, $p < .10$). In the Go > false alarm contrast, activation in the right anterior frontal cortex was marginally related to NoGo trial accuracy ($r = -.51$, $p < .10$). We attribute the lack of statistical significance at traditional thresholds in these correlations to the small sample rather than to small effect sizes; indeed, the observed effect sizes are in the medium range. No other regional correlations with inhibitory control performance approached significance ($p > .10$).

Discussion

In a nonclinical sample of adolescents from families at risk for substance use and antisocial behavior, significant functional activation differences related to inhibitory control were found between adolescents with prenatal exposure to a variety of substances and those without such exposure. fMRI analyses revealed significant group differences in activation in the three contrasts of interest (NoGo > Go, NoGo > false alarm, and Go > false alarm). Simple effects revealed that group differences were consistently driven by relatively increased activation in the exposed group for correct trials (both NoGo and Go) and decreased magnitude of activation in the exposed group for false alarm trials. The between group differences included altered processing in both frontal (e.g., right ventrolateral prefrontal cortex (vlPFC) and right anterior prefrontal/middle prefrontal) and posterior (e.g., cuneus, fusiform gyrus) regions. These results are consistent with the hypothesis that a group of adolescents with heterogeneous prenatal substance exposure would demonstrate altered inhibitory control processing during both correct and incorrect trials. Broadly, the results suggest that adolescents with prenatal exposure have different neural patterns of metabolic expenditure during an inhibitory control task, consistent with a more immature developmental profile.

The results examining exposure-related activation differences of prefrontal regions are consistent with previous research examining prenatal exposure to individual substances (e.g., alcohol, cocaine, methamphetamines). The NoGo > Go contrast analyses identified increased exposure-related activation to NoGo trials in the right ventrolateral prefrontal cortex (otherwise known as the inferior frontal cortex; Aron, Robbins, & Poldrack, 2004). This region is established to be part of the executive attention network, which is critically used in response inhibition and is activated during inhibitory control tasks throughout development and adulthood (Aron et al., 2004; Ordaz, Foran, Velanova, & Luna, 2013). Previous research in young adults prenatally exposed to marijuana also found increased right ventrolateral prefrontal cortex activation associated with prenatal exposure (Smith et al., 2004), although research in adolescents prenatally exposed to alcohol found the opposite pattern. Notably, the substantial majority of studies find increased activation in frontal areas associated with prenatal exposure across substances, including alcohol (reviewed in Derauf et al., 2009; reviewed in Norman, Crocker, Mattson, & Riley, 2009).

In the NoGo > false alarm contrast, analyses indicated significant group differences in the right fusiform gyrus, left cuneus, and right precuneus. These results are difficult to interpret based on the previous literature, because prior research on prenatally exposed adolescents has not examined false alarms and the role of error processing. However, research examining the NoGo > Go contrast have found activation differences in similar brain regions (i.e., right occipital lobe and bilateral cuneus/precuneus) between prenatally exposed and nonexposed adolescents and adolescents across substances (age 8–18; Fryer et al., 2007; Sheinkopf

et al., 2009; Ware et al., 2015). Differential processing in the occipital regions (e.g., the fusiform gyrus and cuneus) are believed to relate to atypical visual sensory processing, which has been associated with prenatal exposure (Fryer et al., 2007). Notably, previous research comparing child to adult samples has found that more mature inhibitory control processing is associated with an exaggerated occipital response to false alarm trials, similar to what was observed here in the nonexposed group (Braet et al., 2009). Across all areas of activation comparing NoGo > false alarm trials, simple effects analyses revealed a pattern of results in which the nonexposed group exhibited differential activation between NoGo and false alarm trials, while the exposed group exhibited minimal differences between trial types. Thus, the nonexposed group may be able to allocate cognitive resources (reflected in increased activation) related to errors more flexibly, compared to the exposed group.

In the Go > false alarm contrast, between group activation revealed differential brain activation in the right anterior prefrontal cortex. Differential inhibitory control processing in this region has not been previously reported in relation to prenatal substance exposure, but the results are similar to those in the NoGo > false alarm contrast. Between group differences appear driven by differential activation to false alarm vs. Go trials in the nonexposed group, compared to the exposed group (with minimal differences between trial types). The right anterior prefrontal cortex has been previously linked to conflict monitoring processes, and so the lack of trial type differentiation in the exposed group could be linked to reduced conflict monitoring, which is an important skill underlying inhibitory control (Power & Petersen, 2013; Wager et al., 2005).

The final analytic step was to examine the association between adolescents' inhibitory control performance (NoGo % accuracy) and activation of brain regions with between group differences. Results indicated that there were no significant associations between performance indices and the identified clusters of brain activation; however, there were multiple marginally significant associations. Specifically greater activation across brain regions [right ventrolateral prefrontal cortex (NoGo > Go contrast); left cuneus (NoGo > false alarm contrast); right middle frontal cortex (Go > false alarm contrast)] was marginally related to poorer inhibitory control performance. We refrain from substantial interpretation of these results due to nonsignificance, but note that, if consistently replicated, these results would suggest that increased activation is associated with performance deficits as opposed to performance gains. Most importantly, the marginally significant findings in this small sample highlight the potential importance of examining brain–behavior differences in future fMRI research to understand better neural profiles associated with behavioral impairment.

The present research has noted limitations and results should be interpreted in consideration of these challenges. First and foremost, the presented findings are from a very small sample of adolescents, which may increase the likelihood of type 1 errors, and should be replicated and extended in a larger sample. However, we believe this limitation to be somewhat offset by the unusual nature of the sample, which includes adolescents drawn from both exposed and nonexposed families recruited from the same larger pool of at-risk families. This limitation is further mitigated by the fact that this research is the first fMRI study of prenatal exposure to include adolescents with such heterogeneity of exposure. As noted by Lieberman and Cunningham (2009), research in smaller sample sizes, with more liberal statistical thresholds, can have particular utility in exploratory research in order to enable discovery of possible effects that can serve as a stepping stone for future replications and extensions. An additional limitation may be maternal retrospective reporting of substance use during pregnancy. However, multiple studies have found that retrospective reports (13 months to 14 years post-partum) may actually be more accurate than concurrent prenatal reports due to the stigmatization of substance use during pregnancy and concurrent maternal denial/distortion (Hannigan et al., 2010; Jacobson et al., 1991). Because adolescents with any level of maternal-reported prenatal substance use were included in the exposed group, potential confounds from retrospective reports should be minimized. Finally, because the sample's sociodemographic characteristics are relatively narrow (i.e., drawn from an at-risk sample, entirely Caucasian), results may have limited generalizability.

In a sample of adolescents prenatally exposed to a range of substances, functional brain activation differences were found in a number of frontal, parietal, and occipital regions during an inhibitory control task. Notably, the effects of prenatal exposure appeared to be present in brain regions established to be particularly critical for inhibitory control (e.g., right ventrolateral prefrontal cortex, left inferior parietal cortex) as well as regions more broadly associated with sensory processing (e.g., occipital lobe) that are similar to those found in research in exposed samples examining different cognitive skills (i.e., working memory). The activation differences were driven by exaggerated activation in the exposed group during correct trials (Go and NoGo) and reduced activation in the exposed group for

incorrect inhibitory control trials (false alarm). Finding differences in a group with such heterogeneous prenatal exposure suggests that prenatal substance exposure may either (1) affect similar neural pathways related to atypical inhibitory control processing, or (2) affect variable neural processes, which result in similar patterns of atypical inhibitory control processing.

Future fMRI research should seek to better understand the common developmental consequences for individuals with heterogeneous prenatal exposure, particularly given that only ~50% of individuals experience single substance exposure. It may be valuable for future research with larger samples to investigate the extent to which heterogeneous prenatal exposure (regarding substance type, dosage, and timing) differences predict variable outcomes, but it may be equally useful to establish common consequences given the theorized overlapping mechanisms of fetal insult (e.g., reduced cerebral blood flow). Although the current control group of nonexposed participants was well-matched to the prenatally exposed group regarding sociodemographic risk and familial history (e.g., fathers at-risk for delinquency, low maternal education), future research in at-risk samples could benefit from a third "low risk" nonexposed control group that may exhibit higher inhibitory control performance and associated differences in neural patterns.

Clinically, the results presented here from a small sample imply that interventions designed to improve inhibitory control skills in adolescents with prenatal exposure to specific substances may be applicable to the broader exposed population (Kalberg & Buckley, 2007). Although some of the impairment in inhibitory control may be related specifically to the atypical functioning of key inhibitory control brain regions, the differences in brain regions associated with sensory processes suggest that more basic neurocognitive impairment may also be present and associated with inhibitory control ability. A better understanding of the relationship between brain activation and behavior is critical to establish the importance of brain activation differences and possible paths to inhibitory control improvement.

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