Behavioural Brain Research 278 (2015) 137–146

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure

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HIGHLIGHTS

- Examined neural function of response inhibition in prenatal alcohol exposure.
- Exposure resulted in greater prefrontal and subcortical activation.
- Greater BOLD was especially related to increased task difficulty.
- Exposed youth with FAS trended towards greater BOLD response than those without FAS.
- Results suggest that this exposure disrupts fronto-striatal circuitry.

ARTICLE INFO

Article history:
Received 28 May 2014
Received in revised form
21 September 2014
Accepted 23 September 2014
Available online 2 October 2014

Keywords:
fMRI
Fetal alcohol spectrum disorders (FASD)
Fetal alcohol syndrome (FAS)
Prenatal alcohol exposure
Response inhibition

ABSTRACT

Heavy prenatal alcohol exposure results in a range of deficits, including both volumetric and functional changes in brain regions involved in response inhibition such as the prefrontal cortex and striatum. The current study examined blood oxygen level-dependent (BOLD) response during a stop signal task in adolescents (ages 13–16 y) with histories of heavy prenatal alcohol exposure (AE, $n = 21$) and controls (CON, $n = 21$). Task performance was measured using percent correct inhibits during three difficulty conditions: easy, medium, and hard. Group differences in BOLD response relative to baseline motor responding were examined across all inhibition trials and for each difficulty condition separately. The contrast between hard and easy trials was analyzed to determine whether increasing task difficulty affected BOLD response. Groups had similar task performance and demographic characteristics, except for full scale IQ scores (AE < CON). The AE group demonstrated greater BOLD response in frontal, sensorimotor, striatal, and cingulate regions relative to controls, especially as task difficulty increased. When contrasting hard vs. easy inhibition trials, the AE group showed greater medial/superior frontal and cuneus BOLD response than controls. Results were unchanged after demographics and FAS diagnosis were statistically controlled. This was the first fMRI study to utilize a stop signal task, isolating fronto-striatal functioning, to assess response inhibition and the effects task difficulty in adolescents with prenatal alcohol exposure. Results suggest that heavy prenatal alcohol exposure disrupts neural function of this circuitry, resulting in immature cognitive processing and motor-association learning and neural compensation during response inhibition.

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1. Introduction

A common clinical observation in neurodevelopmental populations is the inability to withhold strong response tendencies that are contextually or socially inappropriate. Response inhibition (RI) involves suppressing initial prepotent responses, stopping ongoing responses, and guarding a period of delay from competing responses [3]. RI represents a necessary precursor of

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http://dx.doi.org/10.1016/j.bbr.2014.09.037
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goal-directed behavior [3,47] that is distinguishable from other executive functions [26,27]. Clinical and preclinical studies support RI deficits following heavy prenatal alcohol exposure [17,37] through increased perseveration [54], impaired inhibitory control [43], and hyperactivity [53]. Children with histories of this exposure exhibit behavioral disinhibition, resulting in increased secondary deficits such as disruptive disorders, academic failure, and social complications [41,48,62,64]. RI deficits may contribute to global executive dysfunction [2], a hallmark deficit in alcohol-affected children (reviewed in [37]).

Neuroimaging studies illustrate alcohol's teratogenicity on frontal–subcortical structure and function; macro- and microstructural aberrations exist in frontal, subcortical, and white matter regions [33,78]. Caudate and putamen volumes are disproportionately reduced in alcohol-exposed children and correlate with IQ and perseverative errors during inhibition [24,56]. Electrophysiological and functional MRI (fMRI) findings of Go/No-Go (GNG) performance support altered frontal–striatal functioning in children with prenatal alcohol exposure [5–7,68]. Event-related potential (ERP) findings indicated that alcohol-exposed youth exhibited slower wave latencies and smaller wave amplitudes during GNG than controls, suggesting impaired early visual processing and stimulus discrimination, increased cognitive effort, and alternate frontal inhibitory recruitment [5–7,68]. fMRI findings of greater BOLD response in medial and middle frontal regions during GNG relative to performance-matched controls corroborate inefficient frontal functioning in this population although differences in subcortical recruitment during RI are conflicting [23,49].

Since executive control, which includes RI, relates to behavioral dysfunction in alcohol-affected children [41,62,75], understanding the neuropathology underlying RI deficits in this population will increase specificity of known deficits and promote effective interventions. The current study examined RI using the stop-signal task (SST), which may measure different components of RI than GNG. Though generally assumed to measure similar aspects of RI, recent literature indicates benefits of the SST over GNG to assess RI [60,69]. Despite some commonalities, the SST and GNG utilize disparate neural systems [69]; the SST involves frontal–striatal circuits whereas GNG is frontal-parietal dependent. Distinct neural patterns suggest that GNG provides a measure of stimulus learning and action selection relative to SST, which may more accurately measure action cancellation, or RI [63,69]. Discrete task design may contribute to these differences in as much as the SST requires inhibition of ongoing, initiated motor responses instead of action withholding [63,69].

Since prefrontal and striatal brain regions may be especially sensitive to heavy prenatal alcohol exposure, the current investigation of neural correlates of motor RI utilizing the SST in this population may further elucidate compensatory mechanisms utilized by this population. Given previous findings of disrupted frontostriatal structure and function (of greater BOLD response during GNG performance) in alcohol-exposed compared to nonexposed youth, we expected greater BOLD response in alcohol-exposed adolescents relative to controls in prefrontal, subcortical, and cingulate regions, which are recruited during SST performance [23,49,59,63,69].

2. Materials and methods

Two groups ($N = 42$) of adolescents between 13 and 16 years of age were recruited to the Center for Behavioral Teratology at San Diego State University: those with histories of heavy prenatal alcohol exposure (the AE group) and controls (the CON group). Both male and female subjects were eligible for participation and were recruited through referrals from area healthcare providers, other professionals, and community outreach. Estimates of full scale IQ (FSIQ), from the Wechsler Intelligence Scale for Children (WISC-IV) [77], and socioeconomic status, from the Hollingshead Four Factor Index of Social Status [31], were collected as part of a larger project. Informed assent and consent were obtained prior to participation and subject incentive was provided to all subjects. The Institutional Review Board (IRB) at San Diego State University and University of California San Diego approved all procedures.

2.1. Subjects

The AE group ($n = 21$) comprised adolescents with histories of heavy prenatal alcohol exposure, defined as an average of $\geq$14 drinks per week or $\geq$4 alcoholic drinks per occasion at least once per week during gestation. Prenatal exposure was confirmed retrospectively through medical history, birth records, social services records, and maternal report and questionnaires, when available. In most cases, precise measures of alcohol consumption were unavailable. In these cases, mothers were reported to be "alcoholic" or alcohol abusing or dependent during pregnancy. All subjects were evaluated by a dysmorphologist with expertise in Fetal Alcohol Syndrome (FAS) (KLJ). Seven (33%) subjects in the AE group were diagnosed with FAS [32,40]. Additionally, seventeen (81%) subjects in the AE group met DSM-IV criteria for attention deficit/hyperactivity disorder (ADHD) as determined by the clinician-assisted National Institute of Mental Health Diagnostic Interview Schedule for Children (C-DISC-4.0) [65].

The CON group ($n = 21$) consisted of adolescents with minimal or no prenatal alcohol exposure, defined as an average of $\leq$1 drink per week and never more than 2 drinks on a single occasion during gestation. Controls were excluded if they met subclinical or clinical criteria for ADHD. Exclusion criteria for both groups were history of significant head injury or loss of consciousness >30 min, non-fluent English speaker, psychiatric (i.e., active psychosis, pervasive developmental disorder) or physical (i.e., neurological disorders) disability preventing participation, MRI contradictions (i.e., metal in body, claustrophobia), or adopted from abroad after 5 years of age or $\leq$2 years before assessment.

2.2. Mock scan procedure

Prior to MRI scanning, all subjects underwent a mock MRI at the Center for Behavioral Teratology, San Diego State University. Mock procedures were the similar to actual fMRI protocol and included a pre-training session, a 10-min mock anatomical scan during which subjects watched a movie and were trained to remain still, and an 8 min 20 s SST. Mock procedures have successfully decreased data loss resulting from motion artifact in this population (unpublished findings).

2.3. Stop-signal fMRI task

The event-related SST employed in the current study, based on that described by Matthews et al., has been successfully used to examine neural correlates of RI in other adolescent populations [35,36]. During the task (shown in Fig. 1), visual stimuli were projected at a visual angle of approximately 85° onto a white projection screen at the foot of the MRI bed. Stimuli were white capital letters (X or O) displayed on a black background. Subjects were told to press the right button as quickly and as accurately as possible whenever an "O" appeared, the left button whenever an "X" appeared, and not to press either button whenever they heard a tone during a trial. Stimuli appeared at the beginning of each trial, which lasted 1300 ms or until the subject responded. Trials were separated by a 200 ms interstimulus interval (blank screen). Subjects performed six blocks of 48 trials (12 Stop and 36 Go trials in each block). Stop trials were pseudorandomized and counterbalanced. The Go trials

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