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Research report

Anterior cingulate cortex surface area relates to behavioral inhibition in adolescents with and without heavy prenatal alcohol exposure

Robyn Migliorini[a,b,*], Eileen M. Moore[a], Leila Glass[a,b], M. Alejandra Infante[a,b], Susan F. Tapert[c,d], Kenneth Lyons Jones[e], Sarah N. Mattson[a], Edward P. Riley[a]

[a] Center for Behavioral Teratology, Department of Psychology, San Diego State University, 6330 Alvarado Court, Suite 100, San Diego, CA 92120, USA
[b] San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, 6363 Alvarado Court, Suite 103, San Diego, CA 92120-4913, USA
[c] Department of Psychiatry, University of California, San Diego, 9500 Gilman Dr., San Diego, CA 92037, USA
[d] VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA
[e] University of California, San Diego, School of Medicine, Department of Pediatrics, 9500 Gilman Drive, San Diego, CA 92093, USA

HIGHLIGHTS

- Prenatal alcohol exposed youth had reduced anterior cingulate (ACC) surface area.
- Exposure associated with slow inhibition speed but no differences in accuracy.
- Relations between ACC and inhibition speed differed based upon exposure history.
- Smaller ACC area related to slower inhibition speed but only in exposed youth.
- Smaller ACC area related to faster processing speed but only in control youth.

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ABSTRACT

Prenatal alcohol exposure is associated with behavioral disinhibition, yet the brain structure correlates of this deficit have not been determined with sufficient detail. We examined the hypothesis that the structure of the anterior cingulate cortex (ACC) relates to inhibition performance in youth with histories of heavy prenatal alcohol exposure (AE, $n = 32$) and non-exposed controls (CON, $n = 21$). Adolescents (12–17 years) underwent structural magnetic resonance imaging yielding measures of gray matter volume, surface area, and thickness across four ACC subregions. A subset of subjects were administered the NEPSY-II Inhibition subtest. MANCOVA was utilized to test for group differences in ACC and inhibition performance and multiple linear regression was used to probe ACC-inhibition relationships. ACC surface area was significantly smaller in AE, though this effect was primarily driven by reduced right caudal ACC (rcACC). AE also performed significantly worse on inhibition speed but not on inhibition accuracy. Regression analyses with the rcACC revealed a significant group × ACC interaction. A smaller rcACC surface area was associated with slower inhibition completion time for AE but was not significantly associated with inhibition in CON. After accounting for processing speed, smaller rcACC surface area was associated with worse (i.e., slower) inhibition regardless of group. Examining processing speed independently, a decrease in rcACC surface area was associated with faster processing speed for CON but not significantly associated with processing speed in AE. Results support the theory that caudal ACC may monitor reaction time in addition to inhibition and highlight the possibility of delayed ACC neurodevelopment in prenatal alcohol exposure.

* Corresponding author at: 6330 Alvarado Court, Suite 100, San Diego, CA 92120, USA. Tel.: +1 619 594 3929; fax: +1 619 594 1895.
E-mail address: ramiglio@ucsd.edu (R. Migliorini).

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1. Introduction

Gestational alcohol exposure can result in adverse physical, neurological, cognitive, and behavioral consequences for the developing embryo and fetus. Fetal alcohol syndrome (FAS), a phenotype defined by a pattern of craniofacial dysmorphia, growth deficiencies, and central nervous system abnormalities is one of the more severe outcomes of prenatal alcohol exposure [1,2]. However, neurobehavioral deficits may be present even among individuals without all of the features required for FAS [3,4]. The non-diagnostic umbrella term fetal alcohol spectrum disorders (FASD) encompasses the broad range of clinical outcomes associated with prenatal alcohol exposure [5].

Impaired executive functioning, a construct including inhibitory control, cognitive flexibility, working memory, and sustained and selective attention [6] is thought to be a key feature of the neurobehavioral profile of FASD [7]. Here we focus on response inhibition, one aspect of executive functioning, conceptualized as the voluntary suppression of an automatic or impulse-driven action. On neuropsychological measures of response inhibition, prenatally alcohol-exposed individuals tend to demonstrate poor performance. For example, alcohol-exposed children were slower to complete inhibition tasks and made a greater number of inhibition errors relative to non-exposed controls [8] and also as compared to the normative mean score derived from the measure's standardization sample [9]. Significant inhibition deficits have been documented over and above deficits in component skills such as word reading or color naming [8] and may not simply be attributable to lower IQ [10]. Analogous inhibitory deficits have also been reported in animal models of FASD [11–14].

Inhibitory control is critical for successful self-regulation and the completion of non-impulsive goal oriented behavior [15]. Disinhibition in childhood may lead to difficulties with social skills [16], academic functioning [17], and adolescent alcohol use [18]. Compromised impulse control may also contribute to the higher rates of disruptive behavior disorders [19] and attention-deficit/hyperactivity disorder (ADHD) [20,21] observed in alcohol-exposed children. While such problems are prominent in FASD, observations indicate that there may be treatment resistance or atypical treatment response to psychostimulant medications typically used to target impulsivity and related attention problems in children [22]. Understanding the neural underpinnings of inhibition in FASD may lead to the development of better treatment strategies for alcohol-exposed children with inhibitory deficits.

Neuroimaging studies of inhibition often focus on the anterior cingulate cortex (ACC), a medial region in the frontal cortex thought to be responsible for inhibitory processing and conflict/error monitoring. This is supported by a robust literature detailing increased ACC functional activation during inhibition tasks in healthy adults (e.g., [23–27]), typically developing children [28,29] and children with disorders that involve prominent impulse control difficulties such as ADHD [30], autism [31] and disruptive behavior disorders [32]. There is also mounting evidence that the structure of the ACC relates to inhibitory abilities. For example, Takeuchi and colleagues [33] demonstrated that greater ACC volumes were associated with better performance (speed and accuracy combined) on a Stroop interference task in healthy young adults. In healthy children, the sulcal pattern of the ACC predicted inhibitory speed later in development [34] but had no effect on inhibitory accuracy. ACC structure is also associated with children's cognitive control, a broader executive functioning construct that encompasses response inhibition. For instance, youth with larger right ACCs were faster and more accurate on a task of controlled attention performance [35]. Moreover, ACC cortical surface area accounted for a significant proportion of variance in typically-developing children's cognitive control performance and greater surface area was related to faster performance for younger children (<12 years old) [36].

Neuroimaging studies of response inhibition in FASD have almost exclusively focused on the functional correlates of inhibition. In this vein, two functional magnetic resonance imaging (fMRI) studies of inhibitory control using a go-no go task found increased blood oxygen level dependent (BOLD) response in the ACC and surrounding prefrontal and parietal regions, suggesting inefficient or immature processing in inhibitory fronto-parietal networks [37,38]. A more recent investigation using the stop signal task explored BOLD activation to inhibition conditions of varying difficulty in alcohol-exposed and non-exposed adolescents. Group differences in ACC and middle cingulate brain response were specific to the most difficult and demanding inhibition trials [39]. In addition, inhibition accuracy on the stop signal task was positively related to BOLD activation in the middle cingulate in both groups [39].

Although structural alterations in gray matter volume [40], white matter microstructure [41], and neuroanatomical maturation [42] have been reported in alcohol-exposed children, to our knowledge only one study to date has focused on the structural correlates of inhibitory control. Bjorkquist and colleagues examined the structure of the cingulate gyrus and found reduced gray and white matter volumes in alcohol-exposed children [43]. However, after adjusting for total brain volume to account for microcephaly associated with prenatal alcohol exposure, only cingulate white matter remained significantly reduced. Importantly, volumes analyzed in this study were parcellated into anterior and posterior anterior cingulate only, and thus may have been less sensitive to smaller subregional differences within the ACC. In addition, other structural variables such as cortical thickness and surface area were not examined. In cortical brain regions such as the ACC, volume is the product of cortical thickness and cortical surface area. Thickness and surface area are thought to be phenotypically and genetically independent [44–46], follow distinct developmental trajectories, and reach peak size at different stages of childhood and adolescence [47]. Thus, in measuring volume, signal from these independent metrics may be diluted and more subtle structural differences may go undetected.

The neurobehavioral effects of poor inhibition may be widespread in children with prenatal alcohol exposure, yet the neural basis underlying this deficit has not been adequately explored. We sought to examine whether the structure of the ACC related to behavioral performance on a standardized neuropsychological measure of inhibitory control in adolescents with prenatal alcohol exposure. While the majority of structural neuroimaging studies in FASD have focused on volumetric differences, we chose to examine volume, cortical surface area, and cortical thickness variables to gain a more comprehensive understanding of ACC neural structure.

On neuropsychological measures, we expected alcohol-exposed youth to demonstrate poorer inhibition completion time and inhibition error scores compared to non-exposed children, consistent with previous findings [8]. For the neuroimaging measures, we hypothesized that alcohol-exposed adolescents would have reduced ACC volume compared to non-exposed controls, as frontal lobe size reductions are a consistent finding in FASD [40]. This hypothesized difference in volume could be due to underlying differences in ACC surface area, ACC cortical thickness, or both. In light of recent findings suggesting that prenatal alcohol exposure impacts surface area to a greater degree than cortical thickness [48] as well as inconsistent reports of cortical thickness alteration in FASD (e.g., [49,50]), we predicted that alcohol-exposed adolescents would have reduced ACC area but not thickness. Finally, we expected that smaller ACCs would be associated with worse inhibition time and accuracy in both groups, as smaller ACC volume and