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Altered functional connectivity during spatial working memory in children with heavy prenatal alcohol exposure

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ABSTRACT

Individuals prenatally exposed to alcohol often have impaired spatial working memory (SWM). This study examines functional connections of frontal and parietal regions that support SWM in children with and without prenatal alcohol exposure. Children ages 10 to 16 with histories of heavy prenatal alcohol exposure (AE group; n = 18) and controls (CON group; n = 19) underwent functional magnetic resonance imaging (fMRI) while performing a SWM task. Whole brain task-related functional connectivity of bilateral dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) seed regions were estimated for each participant using a psychophysiological interaction approach. Children in the AE group were less accurate than children in the CON group when performing the SWM task ($p = 0.008$). Positive coupling between bilateral DLPFC seeds and regions within the fronto-parietal network was observed in the CON group, whereas the AE group showed negative connectivity. In contrast to the CON group, the AE group showed positive connectivity between PPC seeds and frontal lobe regions. Across seeds, decreased negative coupling with regions outside the fronto-parietal network (e.g., left middle occipital gyrus) were observed in the AE group relative to the CON group. Functional data clusters were considered significant at $p < 0.05$. Overall findings suggest that localized alterations in neural activity, aberrant fronto-parietal network synchrony, and poor coordination of neural responses with regions outside of this network may help explain SWM deficits in individuals with a history of heavy prenatal alcohol exposure.

Introduction

Deficits in working memory have been consistently reported in children with fetal alcohol spectrum disorders (FASDs) (Aragón et al., 2008; Burden, Jacobson, Sokol, & Jacobson, 2005; Green et al., 2009; Hemington & Reynolds, 2014; Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Paolozza et al., 2014; Quattlebaum & O'Connor, 2013; Rasmussen, Soleimani, & Pei, 2011). Furthermore, executive function and spatial processing have been found to be among the most sensitive to prenatal alcohol exposure (Mattson, Roesch, et al., 2010). Thus, it is not surprising that measures of spatial working memory (SWM), the temporary storage of spatial locations for further manipulation (Baddeley, 1986), is impaired in individuals affected by heavy prenatal alcohol exposure (Green et al., 2009; Rasmussen et al., 2011).

A fronto-parietal network, including the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), has been implicated in SWM (van Asselen et al., 2006; Nee & D'Esposito, 2015; Wager & Smith, 2003). Evidence from functional Magnetic Resonance Imaging (fMRI) studies suggests aberrant patterns of activation in response to SWM among individuals with FASD. Specifically, Malisza et al. (2005) found increased activation in inferior and middle frontal brain regions in both children and adults prenatally exposed to alcohol, relative to controls. Conversely, control participants showed significantly greater activity in superior frontal and parietal brain regions. In addition to increased activation patterns, alcohol-exposed children also exhibited decreased activity in the frontal lobe with increasing task difficulty, while the opposite pattern was observed among control children. In a subsequent study, Spadoni et al. (2009) found that

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youth with heavy prenatal alcohol exposure showed greater blood oxygen level dependent (BOLD) response to SWM relative to vigilance trials in frontal, insular, superior and middle temporal, occipital, and subcortical regions compared to controls, despite no significant group differences in task performance. Malisza et al. (2012) compared brain activation patterns during a SWM task in children with alcohol-related neurodevelopmental disorder (ARND), children with attention-deficit/hyperactivity disorder (ADHD), and non-exposed controls. Children with ARND had greater activation in the DLPFC and PPC in comparison to children with ADHD and non-exposed controls. A more recent study examined the neural correlates of SWM in children with heavy prenatal alcohol exposure, non-exposed children with a confirmed family history of alcohol-use disorders, and non-exposed controls (Norman et al., 2013). In comparison to non-exposed control children, children prenatally exposed to alcohol had increased activation in four clusters that included areas of the left middle and superior frontal gyrus, lingual gyrus and cuneus, lentiform nucleus and insula, and the right middle frontal gyrus. Compared to non-exposed children with a positive family history of alcohol-use disorders, the alcohol-exposed group showed greater BOLD response in the left middle frontal gyrus, and right cuneus and precuneus.

These fMRI studies focused on the localization of brain regions that are active during specific tasks. However, identifying patterns of functional interaction between brain regions is critical, given that no specific brain region works in isolation (Fox et al., 2005; McIntosh, 2000). Importantly, functional connectivity can be measured during rest and task conditions. Disturbances in resting state functional connectivity have been reported among individuals prenatally exposed to alcohol (Santhanam et al., 2011; Wozniak et al., 2011, 2013, 2016). Wozniak et al. (2011) examined inter-hemispheric functional connectivity in children prenatally exposed to alcohol in comparison to demographically similar controls. Specifically, the authors focused on brain regions known to have white matter alterations at the microstructural level. Findings indicated lower inter-hemispheric connectivity in paracentral regions in the alcohol-exposed group as compared to the non-exposed control group (i.e., the correlations between contralateral paracentral BOLD response were lower in the FASD group than in the control group). A more recent resting state functional connectivity study examined global cortical connectivity in children prenatally exposed to alcohol relative to non-alcohol exposed controls (Wozniak et al., 2013). The results revealed altered network connectivity in children with prenatal alcohol exposure that indicated overall less efficient brain circuitry. In a resting state connectivity study of adults with prenatal alcohol exposure compared to healthy controls (Santhanam et al., 2011), alcohol-exposed adults displayed reduced connectivity between the middle prefrontal cortex and posterior cingulate cortex, regions within the default mode network, relative to control participants. Moreover, recent research suggests that some of these abnormalities may appear in infancy (Donald et al., 2016). Far less research in FASD has focused on examining functional connectivity of neural networks during task performance. Using simple correlational analysis between BOLD signal fluctuations to measure connectivity during a working memory task, Roussotte et al. (2012) found that compared to non-exposed controls, children with prenatal alcohol exposure showed greater connectivity between putamen seeds and frontal areas, but decreased connectivity with caudate seeds. While these findings suggest altered corticostriatal connectivity, the methodological approach used does account for specific task-related correlations in neural activity between brain regions. Rather, the observed correlations may actually have been a function of non-task-related spontaneous BOLD signal activity. Psychophysiological interactions (PPI), a form of context-dependent connectivity, is a technique that allows for the examination of connectivity between two brain areas as a specific function of the task of interest (or context) (Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). A revised version of the original PPI approach known as generalized psychophysiological interactions (gPPI) has been developed to assess how the connectivity changes for each task condition relative to the implicit baseline, thus allowing for the use of more than two task conditions in the same PPI model and for improved model fit (McLaren, Ries, Xu, & Johnson, 2012). No studies to date have used this approach to examine task-based functional connectivity in FASD.

This study aims to expand on previous studies using gPPI analysis to examine the impact of prenatal alcohol exposure on the functional connectivity associated with SWM. Specifically, we examined connectivity between DLPFC and PPC seed regions and the rest of the brain. The DLPFC and PPC were selected because these regions have been consistently implicated in tasks of SWM. Based on previous findings of inefficient network connectivity in individuals prenatally exposed to alcohol, it was hypothesized that, relative to non-exposed controls, children prenatally exposed to alcohol would show reduced connectivity of fronto-parietal network regions and other task-related brain regions, including the occipital cortex.

Methods

Participants

Thirty-seven children between the ages of 10 and 16 years ($M = 13.70$, $SD = 2.09$) participated in this study: The subjects were 18 children with histories of heavy prenatal alcohol exposure (AE group), and 19 demographically similar controls with minimal or no prenatal alcohol exposure (CON group). Children and their primary caregivers were recruited through the Center for Behavioral Teratology (CBT) at San Diego State University (SDSU) as part of a larger, ongoing study. A multifaceted recruitment strategy was employed, including referrals from diagnostic clinics and other professionals, and community outreach via advertising at various child-related agencies and venues.

Study participants were evaluated by a pediatric dysmorphologist with expertise in alcohol teratogenesis (K. L. Jones). A diagnosis of Fetal Alcohol Syndrome (FAS) was sufficient to meet study criteria for inclusion in the AE group. FAS diagnosis was based on the presence of two or more key facial features (short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip) and either evidence of growth deficiency (height and/or weight $\leq$10th percentile) or microcephaly (head circumference $\leq$10th percentile) (for details, see Jones et al., 2006; Mattson, Foroud, et al., 2010). Three subjects in the AE group met these criteria for a diagnosis of FAS. When maternal self-report was available, heavy prenatal alcohol exposure was defined as maternal consumption of $\geq$4 drinks per occasion at least once per week or $\geq$13 drinks per week several times during pregnancy. For the remaining subjects in the AE group, mothers were reported to be “alcoholic” or to have had alcohol abuse or dependence during pregnancy. Of note, direct maternal self-report was unavailable for all participants in the AE group, as all of the participants in this group were no longer residing with their biological mothers at the time of study participation.

Participants in the CON group had minimal to no prenatal alcohol exposure, defined as no more than one drink per week on average and never more than two drinks on a single occasion