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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 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 ($p = .008$). 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 $p < .05$. 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.

Keywords

Fetal alcohol spectrum disorders (FASD); spatial working memory; fronto-parietal network; functional connectivity; fMRI

Introduction

Deficits in working memory have been consistently reported in children with fetal alcohol spectrum disorders (FASDs) (Aragon et al., 2008; Burden, Jacobson, Sokol, & Jacobson,

2005b; Carmichael Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Green et al., 2009; Hemington & Reynolds, 2014; 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 et al., 2010b). 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 (Mattson et al., 2010b; Nee & D'Esposito, 2015; van Asselen et al., 2006; Wager & Smith, 2003). Evidence from functional Magnetic Resonance Imaging (fMRI) studies suggest 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 youth with heavy prenatal alcohol exposure showed greater 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., 2013; Wozniak et al., 2016; Wozniak et al., 2011). 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 nonexposed 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. But 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 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: 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 10th percentile) or microcephaly (head circumference 10th percentile) (for details, see Jones et al., 2006; Mattson et al., 2010a). 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 4 drinks per occasion at least once per week or 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 during pregnancy. Because the majority of participants in the CON group resided with their biological mothers, screening for exposure to alcohol or other teratogens was determined through direct maternal self-report in most cases. General exclusion criteria included the following: (1) history of significant head injury with loss of consciousness for more than 30 minutes, (2) evidence of any other known causes of mental deficiency, or significant physical, neurological, or psychiatric disability that would prevent participation in the study, (3) adopted from abroad after the age of five or less than two years before the assessment, and (4) any contraindication for MRI procedure (e.g., metallic implants). In addition, participants were excluded from the CON group if they met diagnostic criteria for a psychiatric illness based on the NIMH Diagnostic Interview Schedule for Children Version IV (C-DISC-4.0) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000).

Written informed parental consent and participant assent were obtained prior to participation. The Institutional Review Boards of SDSU and the University of California San Diego (UC San Diego) approved all study procedures. Participants received a financial incentive for participation in the study.

Procedures

As part of this larger study, a general conceptual ability (GCA) score from the Differential Ability Scales–Second Edition (DAS–II) (Elliott, 2007), which is a composite score related to general reasoning and conceptual abilities that is similar to a Full Scale IQ score, was computed. Socioeconomic status (SES), as measured by the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975), was also determined for all study participants. Prior to the fMRI scan appointment, all participants habituated to the scanning environment using a mock scanner located at the CBT. The mock scanner simulates the actual scanner experience in the absence of a magnetic field. Children were instructed to lie still in the mock scanner while wearing a head band that monitored movement.

Assessment of motion was based on our behavioral observation and the Flock of Birds real time motion tracking system used to monitor participant's head movements (model 6DF0B, Ascension Technology Corp., Burlington, VT). During the mock, children practiced lying still while watching a target on a screen, watching a movie, and with their eyes closed. Verbal feedback regarding motion was provided to participants during the session. The Completion time for the mock scanning session was approximately 30–45 minutes.

Image acquisition—Participants were scanned at the UC San Diego Center for Functional Magnetic Resonance Imaging (CfMRI) on a General Electric Discovery MR750 3.0 Tesla whole body magnet using an 8-channel gradient head coil. A high-resolution T1-weighted anatomical scan was acquired in the sagittal plane using a three-dimensional IR-SPGR (TR = 7.38 ms, TE = 2.98 ms, TI = 640 ms, flip angle = 8 degrees, FOV = 240 mm, frequency = 256, phase = 192, slice thickness 1.2 mm) or MPRAGE (TR = 7.65 ms, TE = 3.04 ms, TI = 900 ms, flip angle = 8 degrees, FOV = 256 mm, frequency = 256, phase = 256, slice thickness 1 mm) pulse sequence with online motion correction. Functional images were acquired in the axial plane using gradient echo EPI (TR = 3000 ms, TE = 30 ms, flip angle = 90 degrees, FOV = 24 cm, frequency = 64, phase = 64, number of slices = 32, slice thickness = 3.8 mm, in plane resolution = 3.75 mm × 3.75 mm, repetitions = 156). Task stimuli were back-projected from a laptop onto a screen at the foot of the scanner bed, and were visible via an angled mirror mounted to the head coil.

fMRI paradigm—The task used during the fMRI session, originally adapted from McCarthy et al. (1994), was designed to probe brain regions subserving SWM (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Tapert et al., 2001). The SWM task (see Figure 1), consisted of three blocks of rest, during which a fixation cross appeared in the center of the projection screen, and 18 experimental blocks (20 s in duration) that alternated between baseline (vigilance) and experimental (SWM) conditions. A 1 s cue word ('LOOK,' 'DOTS,' or 'WHERE') appeared at the center of the screen immediately before each block to indicate the beginning and type of condition. Rest blocks, prefaced by the word 'LOOK,' were followed by 20 s of viewing a cross. Figures presented during the vigilance and SWM conditions consisted of abstract Kimura line drawings (Kimura, 1963). The baseline vigilance condition began with the word 'DOTS,' which cued the participant to press the button every time a dot appeared above a figure, approximately 30% of the time. The vigilance condition allowed for control of visual attention and simple motor processes

involved during SWM. In the SWM condition, figures were individually presented in one of eight locations. The SWM began with the word 'WHERE,' cueing participants to press the button every time a figure appeared in the same location as a previous figure within that block. Of the ten stimuli presented in each block, an average of three were target trials, or figures that were presented in the same location as the figure presented two trials ago (2-back). For each condition, stimuli were presented on the screen for 1000 ms with an inter-trial stimulus interval of 1000 ms. Accuracy and reaction time (RT) data were logged using a response box designed for MRI studies (Current Designs, Pittsburgh, PA).

Statistical analyses

Demographic and behavioral data—Group differences in demographic characteristics (i.e., sex, race, ethnicity, handedness, age, SES, and GCA) were examined using independent samples t-tests and chi-squared tests. A total accuracy cut-off of 69% was set for both task conditions (vigilance and SWM), so that only participants who were engaged during cognitive task performance were included in the analyses. Using these criteria, no participants were excluded based on performance. Total accuracy was calculated as the percentage of correct responses for all trials belonging to the same condition. Similar criteria have been used in prior studies of youth with heavy prenatal alcohol exposure using the same SWM task (Norman et al., 2013; Spadoni et al., 2009). Group differences in vigilance and SWM total accuracy and RT were examined using independent samples t-tests. Analyses were performed using SPSS v. 22.

Imaging data—Functional images were preprocessed and analyzed using the FMRIB software library (FSL) (Smith et al., 2004) and Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Researchers conducting the image processing were blinded to participants' group classification. All T1-weighted images were skull-stripped and registered to MNI-152 standard space using FSL's registration tools FLIRT (Jenkinson & Smith, 2001) followed by non-linear registration using FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b). Next, functional data were visually inspected for scanner artifacts. Distortions caused by inhomogeneities of the magnetic field were corrected using field maps. To correct for small movements over time, image repetitions were registered to a selected base volume via AFNI's 3dvolreg program (Cox & Jesmanowicz, 1999). The time series of the motion parameters were used in the linear regression analysis of individual data to control for spin history effects (Friston, Williams, Howard, Frackowiak, & Turner, 1996). Participants (N = 3, AE group), not described in this sample) were excluded from the analysis if more than 15% of repetitions were discarded due to excessive motion (>4 mm). Next, functional data were resampled into 4 mm isometric voxels, transformed into the subject's anatomical space and aligned to standard space using the previously computed anatomical to MNI152 transformation matrix, and smoothed with a 6 mm FWHM Gaussian kernel. Deconvolution analysis of the fMRI time series data was conducted using AFNI's 3dDeconvolve algorithm. The GLM used reference vectors for the SWM and vigilance conditions convolved with the hemodynamic response function. Estimated motion and linear trends were also included as nuisance variables. The resulting model generated scaled beta coefficient maps representing the mean percent BOLD signal change for each condition of the task relative to fixation and for contrast image of SWM – Vigilance.

Functional connectivity analyses were conducted using gPPI with seeds in the DLPFC and PPC. The selection of seed regions within the bilateral DLPFC and PPC (i.e. regions of the fronto-parietal network) was based on activation to the SWM – vigilance contrast collapsing across all participants, and a priori knowledge of the involvement of these regions in SWM (Glahn et al., 2002; Koch et al., 2005; Owen, McMillan, Laird, & Bullmore, 2005; van Asselen et al., 2006). Activation to the SWM – vigilance contrast was determined for all participants combined using a one-sample t-test with AFNI's 3dttest++ program. Correction for multiple comparisons using a cluster threshold based on Monte Carlo simulations was implemented via AFNI's 3dClustSim. A corrected significance level of $p < .05$ (with an uncorrected voxelwise threshold: $p < .05$; minimum cluster volume: 63 voxels) was used for all analyses. Because the t-test results yielded large clusters of activation covering multiple regions, AFNI's 3dExtrema program was used to identify the local maxima within bilateral DLPFC and PPC from which corresponding seeds were selected. Specifically, activation peaks were located in bilateral middle frontal gyri (right: $x = 35.50$, $y = 28.50$, $z = 34.50$; left: $x = -32.50$, $y = 4.50$, $z = 54.50$), and bilateral superior parietal lobes (right: $x = 27.50$, $y = -51.50$, $z = 50.50$; left: $x = -36.50$, $y = -47.50$, $z = 58.50$). A total of four functional seeds were defined as spheres (5 mm radius) around the local maxima within each region and later used as seeds for the gPPI. Functional seeds were defined as spheres (5 mm radius) around the local maxima within each region. For each participant, the average time series of the BOLD signal was extracted for the four seeds, and trends were removed. A deconvolution of the seed's time series was calculated using the 3dTfitter AFNI program. PPI regressors (interaction terms) for each condition of the task (SWM, vigilance) were computed by multiplying the mean time series of the deconvolved seed with the condition vector of interest, and then convolved with a gamma basis function using the AFNI program Waver. Separate voxelwise GLMs were conducted for each seed. Each GLM contained the PPI regressors, the physiological regressor (seed time series), the psychological regressors (i.e. task condition regressors), and nuisance variables (i.e., the motion regressors from the prior fMRI analysis). The resulting contrast images were transformed into a z-score using Fisher's z transformation for subsequent group level analyses. Each seed's connectivity with other brain areas was examined separately. The z-transformed contrast image was used to denote the strength of the functional connectivity between regions whose task-dependent connectivity with the specific seed changed as a function of SWM. Whole-brain between group differences in functional connectivity were estimated using an independent samples t-test via AFNI 3dttest++. Clusters in the cerebellum were excluded due to unreliable data as a result of partial coverage of this area during scan acquisition.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of study participants are presented in Table 1. There were no significant group differences in terms of sex, $\chi^2(1) = .02$, $p = .886$, race, $\chi^2(4) = 4.92$, $p = .295$, ethnicity, $\chi^2(2) = 3.96$, $p = .138$, handedness, $\chi^2(2) = 2.81$, $p = .246$, age, $t(35) = .49$, $p = .63$, or SES, $t(35) = -1.02$, $p = .313$. As expected, children with heavy prenatal alcohol exposure had significantly lower GCA scores on the DAS-II than non-

exposed controls, $t(35) = -5.92$, $p < .001$. No significant groups differences were found on total intracranial volume, $t(35) = -1.08$, $p = .290$.

Task performance

All participants with usable imaging data ($N = 37$) performed with greater than 69% total accuracy for the vigilance and SWM condition, demonstrating that participants performed better than chance. Group differences were found on SWM total accuracy, $t(35) = -2.82$, $p = .008$, such that the CON group was more accurate ($M = 90.56$, $SD = 6.18$) than the AE group ($M = 83.41$, $SD = 9.05$). Groups did not differ with respect to vigilance total accuracy. The mean RT for correct response for trials in the vigilance and SWM conditions did not differ between groups. Task performance by group is displayed in Figure 2.

gPPI estimates of functional connectivity

Clusters showing significant group differences in functional connectivity in response to the SWM –vigilance contrast (examined via gPPI) using bilateral DLPFC and PPC seeds are described below. The peak activation coordinates and additional information for each significant cluster are presented in Table 2.

Right DLPFC seed—Significant group differences in functional connectivity with respect to the right DLPFC were found in five clusters (see Figure 3). Compared to the CON group, the AE group showed decreased negative connectivity between the right DLPFC seed and clusters encompassing bilateral superior frontal gyri, left inferior temporal gyrus (extending to the fusiform), and left middle occipital gyrus. The CON group showed positive connectivity between the right DLPFC and a cluster with peak connectivity within the right inferior parietal lobule extending to the superior parietal lobule, postcentral gyrus, and medially to the precuneus and paracentral lobule, as well as a cluster encompassing bilateral middle frontal gyri and medial regions (bilateral medial frontal gyri and right cingulate). In contrast, the AE group showed negative connectivity between the seed and these regions.

Left DLPFC seed—In comparison to the CON group, the AE group showed decreased negative connectivity between the left DLPFC and one cluster encompassing bilateral superior frontal gyri, and a cluster in the left middle occipital gyrus. Relative to the AE group, the CON group showed greater connectivity between the left DLPFC and three clusters. These included a right hemisphere cluster with peak connectivity within the inferior parietal lobule, extending to the paracentral lobule, and precuneus, a cluster encompassing the left middle frontal gyrus and medial frontal gyrus, and a cluster in the temporal gyrus extending to the supramarginal gyrus. Regions of significant group differences in connectivity with the left DLPFC are depicted in Figure 4.

Right PPC seed—In comparison to the CON group, the AE group showed decreased negative connectivity between the right PPC seed and a cluster encompassing bilateral middle occipital gyri and cuneus. Positive connectivity between the seed and a cluster encompassing bilateral superior frontal gyri (see Figure 5) was observed in the AE group relative to the CON group. There were no clusters in which the CON group showed positive connectivity with the right PPC seed.

Left PPC seed—Decreased negative functional connectivity between the left PPC seed and four clusters (see Figure 6) was observed in the AE group as compared to the CON group. The largest cluster encompassed bilateral superior frontal gyri extending into middle frontal gyri. Additional clusters were seen in the left middle occipital gyrus extending bilaterally into the cuneus, the right insula and middle frontal gyrus, and the left paracentral lobule and cingulate. Children in the AE group showed increased connectivity between the seed and cluster encompassing the left inferior and middle frontal gyri. There were no clusters in which children in the CON group showed positive connectivity with the seed.

Follow-up analyses—Owing to new standards suggested by Eklund et al., 2016, follow-up whole brain gPPI functional connectivity analyses were conducted using a voxelwise threshold of $p < .01$. Task performance (measured as total accuracy on the SWM ‘where’ condition) and handedness were further included as covariates. While there was a noticeable reduction in the size of clusters observed, along with an increase in the number of significant clusters, the overall results remained largely unchanged. For ease of interpretation results are presented using a voxel-wise threshold of $p < .05$.

While significant group differences were observed in GCA, we chose not include this as a covariate because diminished intellectual capacity is consistently reported in individuals with heavy prenatal alcohol exposure (for review, see Mattson et al., 2011). There are statistical and theoretical arguments against including IQ as a covariate when populations differ on this measure, including the risk of producing overcorrected, non-representative, and counterintuitive findings (Dennis et al., 2009).

Discussion

Children in the CON group performed more accurately on SWM trials than children in the AE group. This is consistent with SWM deficits frequently reported in FASD (Aragon et al., 2008; Burden et al., 2005b; Green et al., 2009; Hemington & Reynolds, 2014; Mattson et al., 2013; Paolozza et al., 2014; Quattlebaum & O’Connor, 2013; Rasmussen et al., 2011). Overall accuracy in the AE group was relatively high at approximately 83%. There were no differences between groups on vigilance accuracy. This suggests that children prenatally exposed to alcohol were not able to perform at the same level as participants in the CON group during the SWM condition despite being actively engaged in the task. No significant group differences were found with respect to RT on either the SWM condition or the vigilance condition, suggesting that differences in performance accuracy could not be explained by slower processing speed, as is typically observed among children prenatally exposed to alcohol (e.g., Burden, Jacobson, & Jacobson, 2005a), but rather indicated deficits in SWM.

The majority of fMRI studies in FASD have focused on the detection of brain activation associated with different cognitive functions (for review, see Moore, Migliorini, Infante, & Riley, 2014). Building on this technique, examining task-based functional connectivity may be an important step towards understanding local changes in brain activity during performance of a task by exploring the neural network in which information is shared and integrated in response to different cognitive processes (Ernst, Torrisi, Balderston, Grillon, &

Hale, 2015). This study explored the brain's functional organization associated with SWM using four seeds within the fronto-parietal network: bilateral DLPFC and bilateral PPC. Group differences in functional connectivity patterns between each seed and all other voxels in the brain were examined using gPPI analysis (McLaren et al., 2012). In contrast to the more traditional measure of functional connectivity, which is based on correlations among measures of neural activity, the use of PPI allows us to measure of the relation or "functional coupling" between two neural regions as a function of the task (Cisler, Bush, & Steele, 2014; Friston et al., 1997). Of note, this is the first study to examine functional connectivity during a SWM task using this type of approach in children with FASD.

As hypothesized, the AE group showed decreased functional connectivity in response to the SWM – vigilance contrast, evidenced by negative coupling between the bilateral DLPFC seeds and clusters encompassing the right inferior parietal lobule. On the contrary, the CON group showed increased connectivity between these regions. Children in the AE group also showed negative connectivity between the DLPFC seed and both ipsilateral and contralateral prefrontal cortex regions, whereas the CON group showed positive connectivity between these regions. Research has shown that functional connectivity between cortical regions is an important marker of cognitive ability (Bullmore & Sporns, 2009; Rychwalska, 2013). A fronto-parietal network has been implicated in top-down control mechanisms required for working memory (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Gazzaley & Nobre, 2012). Alterations in the functional coupling between the DLPFC and the right inferior parietal lobule may underlie SWM deficits in FASD, and suggest possible deficits in the top-down control mechanisms. The observed negative connectivity between these regions in the AE group may be reflective of activity in one brain region suppressing activity in another region (Fox et al., 2005; Friston et al., 1996). However, it should be noted that PPI is a correlational based type of approach, and therefore does not provide information regarding the causal direction between functional coupled regions (O'Reilly et al., 2012).

Functional connectivity analyses with bilateral PPC as seed regions revealed group differences in connectivity primarily in regions within the DLPFC (superior, middle, and inferior frontal gyri). Children in the AE group showed increased connectivity compared to the CON group. These findings are contrary to the hypothesis that decreased connectivity would be found in the AE group. The PPC seeds used in the current study were centered on the peak voxel of clusters within the right and left superior parietal lobe. The superior parietal lobe, along with the DLPFC, has been implicated specifically on the manipulation of information on working memory tasks (Koenigs, Barbey, Postle, & Grafman, 2009). Enhanced positive functional connectivity between the PPC seed and DLPFC regions may suggest a compensatory reallocation of cognitive resources, or less efficient communication of neural regions.

Other areas of significant group differences in functional connectivity were noted outside the fronto-parietal network. This is not surprising given that SWM also involves processing of visual information, and thus requires the coordination of visual cortex areas with the prefrontal cortex. In comparison to the CON group, children in the AE group showed decreased negative functional connectivity between each seed and the left middle occipital gyrus. A possible interpretation concerning SWM deficits in the AE group may be related to

the ineffective inhibition of posterior visual processing areas (i.e., the middle occipital gyrus) required for successful task performance. Previous fMRI studies have shown that deficits in neural suppression may be a key component of selective performance deficits (Bressler, Spotswood, & Whitney, 2007; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). This interpretation is supported by the increased activation found during vigilance trials in contrast to the more challenging SWM trials, demonstrating that children prenatally exposed to alcohol may have experienced the SWM component of the task as more cognitively taxing than those in the CON group. They may, in turn, have necessitated increased recruitment of visual processing regions to complete the task. Other studies also support the possibility that SWM deficits in FASD may be secondary to visual processing, which is consistent with alterations in the bottom-up processing in children with ARND suggested by O'Conaill et al. (2015). For example, a study by Malisz et al. (2012) found decreased occipital activation during a 0-back task in children with ARND relative to controls, indicating inefficient visual processing pathways or compromised visual attention in the ARND group.

Potential limitations of the present study must be noted. The majority of children in the AE group met criteria for at least one psychiatric diagnosis. ADHD was the most common diagnosis in the sample, with 11 (61 %) children meeting diagnostic criteria. It is possible that the abnormal activation and functional connectivity patterns observed in the present study were due to comorbid psychopathology rather than specifically to heavy prenatal alcohol exposure. However, it should also be noted that previous studies have also reported increased rates of psychopathology, such as ADHD, in youth prenatally exposed to alcohol (Fryer, McGee, Matt, Riley, & Mattson, 2007; Ware et al., 2013). Thus, excluding individuals who met criteria for a psychiatric disorder may have diminished the representativeness of the present sample. Additionally, doing so may have limited the generalizability of the present results to only apply to children who have been least affected by prenatal alcohol exposure. Another limitation to consider is that psychotropic medications may have impacted cerebral blood flow, contributing to the altered BOLD signals that were observed. Accordingly, three children in the AE group took psychotropic medication on the same day of their appointment, prior to their scan time. Post hoc analyses indicated that results did not significantly change if data provided by these three children were excluded from analyses; however, it is nonetheless possible that the effect sizes or other statistics may have been impacted. Interpretation of "negative" percent BOLD signal change must be acknowledged as a potential limitation. Finally, although overall accuracy for the SWM trials was relatively high in the AE group (83.41%), this performance was significantly lower than the CON group (90.56%). Thus, it is possible that performance differences may have impacted the fMRI results. However, the clusters that showed significant differences in activation between groups remained significant after accounting for behavioral performance in post hoc analyses.

Overall findings suggest that 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. The present study extends prior work reporting spatial working memory deficits in FASD. Although behavioral data suggested that participants understood the task and were engaged, children in the AE group performed worse than children in the CON group in the SWM condition.

Beyond the behavioral performance, this is the first known study to use gPPI to examine task-based functional connectivity in children with FASD. Results showed altered fronto-parietal network connectivity during SWM, and suggested that children prenatally exposed to alcohol may have struggled to update spatial information necessary for successful completion of the task. This may have been driven by a reliance on posterior regions involving the parietal and occipital cortices. Disruption in the functional connectivity between task-related regions may have been related to alterations in top-down control mechanisms and/or ineffective inhibition of posterior visual processing areas required for successful task performance.

The present study adds to the growing body of research on the neurobiological impact of gestational exposure to alcohol, and advances understanding of the mechanisms underlying cognitive deficits in FASD. Additionally, although further research is needed in this area, this study may help identify potential neurobiological markers of intervention effectiveness. Further research in this population using multimodal imaging is now needed to better understand the pathophysiology of cognitive deficits as result of prenatal alcohol exposure. Replication of these findings with a larger sample will be important to ascertain generalizability. Future studies should examine the potential role that psychiatric disorders (e.g., ADHD) may play in the brain mechanisms of children prenatally exposed to alcohol. Given recent advances in multimodal imaging techniques, future research with a larger sample size should use more precise techniques to study brain function and structure relations in individuals with heavy prenatal alcohol exposure. For example, future studies could use fMRI in combination with DTI probabilistic tractography to study the functional and structural integrity of the fronto-parietal network in children affected by gestational exposure to alcohol. Multimodal fusion applications may also be a promising avenue for future research (e.g., Sui, Huster, Yu, Segall, & Calhoun, 2014). A better understanding of the neural mechanisms that lead to working memory impairments in children with FASD could lead to the development of targeted, and more effective interventions to ameliorate these deficits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Schematic of the Spatial Working Memory task (adapted from Tapert et al., 2001).

Figure 2. Behavioral performance in AE and CON groups on the SWM task. (A) Mean percent accuracy and (B) mean reaction time for SWM and vigilance trials. Error bars indicate standard error of the mean (SEM).

Figure 3. Regions showing group differences in functional connectivity with the right dorsolateral prefrontal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SEM. R = right; L = left; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; SFG = superior frontal gyrus; MFG = middle frontal gyrus; ITG = inferior temporal gyrus; MOG = middle occipital gyrus.

Figure 4. Regions showing group differences in functional connectivity with the left dorsolateral prefrontal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SEM. R = right; L = left; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; SFG = superior frontal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; MOG = middle occipital gyrus.

Figure 5.

Regions showing group differences in functional connectivity with the right posterior parietal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SEM. R = right; L = left; PPC = posterior parietal cortex; MOG = middle occipital gyrus; SFG = superior frontal gyrus.

Figure 6. Regions showing group differences in functional connectivity with the left posterior parietal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SEM. R = right; L = left; PPC = posterior parietal cortex; SFG = superior frontal gyrus; MOG = middle occipital gyrus; INS = insula; PCL = paracentral lobule; IFG = inferior frontal gyrus.

Table 1

Demographic and clinical characteristics of study participants by group

Variable	Group	
	AE (n = 18)	CON (n = 19)
Sex [n (%) Female]	8 (44.4)	8 (42.1)
Race [n (%) White]	10 (55.6)	7 (36.8)
Ethnicity [n (%) Hispanic]	7 (38.9)	3 (15.8)
Handedness [n (%) Right]	14 (77.8)	18 (94.7)
Age in years [M (SD)]	13.9 (2.1)	13.5 (2.5)
SES [M (SD)]	43.8 (12.9)	47.9 (11.4)
GCA [M (SD)] *	85.8 (8.8)	110.6 (15.6)
TIV [M (SD)]	1425321.7 (208140.6)	1493934.6 (179575.3)
FAS Diagnosis [n (%)]	3 (16.67)	—

Note. AE = children with heavy prenatal alcohol exposure; CON = controls; SES = socioeconomic status; GCA = general conceptual ability score; TIV = total intracranial volume.

* Significant at the $p < .001$ level.

Table 2

Regions showing significant group differences in functional connectivity

Seed	Voxels	MNI coordinates			<i>t</i> (35)	Cohen's <i>d</i>
Anatomic location		<i>x</i>	<i>y</i>	<i>z</i>		
R DLPFC						
R inferior parietal lobule	378	40	-40	42	-3.40	-1.15
R superior frontal gyrus	254	32	24	54	3.80	1.28
R top frontal gyrus	189	24	-8	58	-2.39	-0.81
L inferior temporal gyrus	94	-60	-20	-22	3.10	1.05
L top occipital gyrus	77	-20	-100	10	3.61	1.22
L DLPFC						
R inferior parietal lobule	298	36	-40	42	-3.52	-1.19
L superior frontal gyrus	242	-24	20	54	2.70	0.91
L top frontal gyrus	102	-24	-8	50	-2.80	-0.95
R top temporal gyrus	101	32	-64	26	-2.69	-0.91
L top occipital gyrus	84	-20	-100	10	3.47	1.17
R PPC						
L top occipital gyrus	291	-20	-96	10	3.49	1.18
R superior frontal gyrus	149	20	36	50	3.07	1.04
L PPC						
R superior frontal gyrus	1738	20	36	50	3.58	1.21
L top occipital gyrus	655	-20	-96	10	3.37	1.14
R insula	210	40	8	22	3.08	1.04
L paracentral lobule	88	-4	-12	46	2.40	0.81
L inferior frontal gyrus	79	-48	16	26	3.85	1.30

Note. Coordinates refer to location of the peak voxel within the cluster. Peak coordinates are reported in MNI152 space. MNI = Montreal Neurological Institute; R = right; L = left; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex.