Functional connectivity of the attention networks is altered and relates to neuropsychological outcomes in children with prenatal alcohol exposure

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ABSTRACT

Cognitive and functional brain alterations can occur in children with prenatal alcohol exposure (PAE). We examined the functional connectivity (FC) among regions within and between attention networks, and whether inter- and intranetwork FC moderated cognition in children with PAE. Participants completed standardized attention and executive functioning tasks and resting state functional MRI. Inter- and intra-network FC and graph-theoretical metrics were calculated among attention network regions. Relative to controls, PAE was associated with reduced FC between the left temporoparietal junction and left ventral frontal cortex and anterior insula/frontal operculum (aI/fO), and between the left intraparietal sulcus and bilateral aI/fO. PAE was associated with increased FC between the right precuneus and intraparietal lobes, the right anterior prefrontal cortex and left ventral frontal cortex and aI/fO, and the left thalamus and dorsal frontal cortex. Graph-theoretical metrics did not differ by group. FC predicted cognitive performance, negatively in the children with PAE and positively in controls. Increased intra-network together with reduced internetwork FC suggests inefficient network specialization and impaired long-range FC among attention network regions after PAE. Results further suggest that those alterations may underlie attention and executive dysfunction in children with PAE.

1. Introduction

Prenatal alcohol exposure (PAE) can lead to fetal alcohol spectrum disorder (FASD), a neurodevelopmental disorder characterized by physical, neuropsychological, and neurological abnormalities (Cook et al., 2016). FASD is estimated to affect 2–5% of the population in North America, with higher prevalence in other parts of the world (Flannigan et al., 2018; Popova et al., 2019). FASD represents a significant economic burden (Popova et al., 2019). A diagnosis of FASD typically requires confirmation of PAE and cognitive, behavioral, and/or emotional dysfunction (specific diagnostic criteria are detailed elsewhere, e.g., Cook et al., 2016). Attention difficulties are a hallmark deficit in children and adolescents with PAE, and these deficits persist into adulthood (Mattson et al., 2019). However, despite mounting evidence for both structural and functional brain alterations in alcohol-exposed children, the neural correlates that give rise to these well-documented attention deficits following PAE are poorly understood.

Attention is supported by a dual brain network system that involves involuntary (bottom-up) and voluntary (top-down) processes (Peterson and Posner, 2012). Involuntary processes are stimulus-driven and rely on stimulus orienting (engaging, disengaging, and shifting attention

Abbreviations: PAE, Prenatal alcohol exposure; FASD, fetal alcohol spectrum disorder; ON, orienting network; ECN, executive control network; ADHD, attention deficit/hyperactivity disorder; ARND, alcohol-related neurodevelopmental disorder; FAS, fetal alcohol syndrome; TD, typically developing; M, mean; SD, standard deviation; NEPSY-II, Developmental Neuropsychological Assessment; BRIEF, Behavior Rating Inventory of Executive Function; TR, repetition time; TE, echo time; rs-fMRI, resting state functional MRI; fMRI, functional MRI; ROI, region-of-interest; dACC, dorsal anterior cingulate cortex; aPFC, anterior prefrontal cortex; mCC, medial cingulate cortex; dFC, dorsal frontal cortex; dFFC, dorsal lateral prefrontal cortex; aI/FO, anterior insula/frontal operculum; IPS, intraparietal sulcus; IPI, intraparietal lobe; TPJ, temporoparietal junction; FEF, frontal eye fields; VFC, ventral frontal cortex; MNI, Montreal Neurological Institute; L, Left; R, Right; FC, functional connectivity; rs-fMRI, resting-state fMRI.

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between salient stimuli). The associated brain regions of the orienting network (ON) include the frontal eye fields, superior parietal lobule, and intraparietal sulcus (the bottom-up, dorsal attention system of the ON), and the temporal parietal junction and ventral frontal cortex (the bottom-up, ventral attention system of the ON; Peterson and Posner, 2012). The executive control network (ECN) underlies the executive attentional processes that are necessary for response control, including voluntary action selection and conflict resolution. Components of the ECN include the dorsolateral prefrontal and superior parietal cortices, thalamus, and cingulate cortex. The ECN processes arise through a top-down frontoparietal control system and a bottom-up cingulo-opercular system (Peterson and Posner, 2012). Alterations within the ECN are associated with the inhibitory deficits observed in primary attention deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder commonly diagnosed in children with PAE (American Psychiatric Association, 2013; Dennis et al., 2008; Infante et al., 2015).

Numerous studies of children with PAE highlight domain-general and specific deficits in attention. Children and adolescents with PAE exhibit greater difficulties with aspects of visual attention relative to auditory attention, with performance on the latter typically similar to that of nonexposed controls (Coles et al., 2002; Mattson et al., 2006). Children with PAE are less efficient and accurate at visual attention tasks than nonexposed controls, as demonstrated by slower reaction time and increased omission errors (Coles et al., 2002; Mattson et al., 2006; Paolozza et al., 2014c). However, rather than global visual attention deficits, impairments in individuals with PAE typically occur in focusing and shifting attention (Coles et al., 1997; Mattson et al., 2006; Paolozza et al., 2013). These findings cumulatively support disruption of the ON. Sustained attention appears to be relatively spared in individuals with PAE, although performance is typically slower and marked by more frequent commission errors than nonexposed controls (Coles et al., 2002; Green et al., 2009; Mattson et al., 2006). However, children with PAE and nonexposed children with primary ADHD-Combined Type have similar conflict resolution difficulties, possibly due to ECN disruption (Kooistra et al., 2010). It is not clear whether the executive attention processing difficulties observed in children with PAE arise from dysfunction of the ECN, the downstream effects of ON dysfunction, internetwork connectivity alterations, or a combination of these (Green et al., 2009). For example, deficits in working memory and inhibitory control common to PAE (Kingdon et al., 2016; Mattson et al., 2019) could be caused by difficulty disengaging and reengaging attention from one stimulus to the next (i.e., increased disengagement cost; altered ON function), especially when information is presented quickly (Kooistra et al., 2009; Migliorini et al., 2015).

The domain-specific pattern of strengths and weaknesses in attention likely results from the congenital brain dysmorphologies and altered neurodevelopmental trajectories that commonly occur in children with PAE (Lebel et al., 2012). The atypical stuctural and development caused by PAE may underlie the documented attention difficulties (Hendrickson et al., 2018; Lebel et al., 2012; Nguyen et al., 2017; Paolozza et al., 2017; Treit et al., 2013). Anomalous brain function following PAE also is shown by functional MRI (fMRI) studies (e.g., Long et al., 2015; Ware et al., 2015). Decreased functional connectivity has been found in children with PAE relative to controls in the bilateral precentral gyrus (Fan et al., 2017), and auditory attention performance is positively correlated with internetwork functional connectivity (i.e., between the left insula and the right posterior superior temporal gyrus) in adolescents with PAE (Little et al., 2017). A task-based fMRI study also found that adults with PAE presented decreased default mode network deactivation during a cognitively demanding task, suggesting weaker attention modulation (Santhanam et al., 2011).

Little research has directly examined the functional correlates of attention networks in children with PAE. Altered functional and structural connectivity of the ventral frontoparietal attention pathway was found along with poor target detection (bottom-up processing) in children with PAE, suggesting ON impairment (O’Conaill et al., 2015). Further examination of the effects of PAE on the functional connectivity of specific attention networks could provide important insights into the neuropathology underlying different aspects of attention in individuals with PAE and could aid in the identification of therapeutic targets and treatment development. In the current study, we used resting-state fMRI (rs-fMRI) in conjunction with neuropsychological measures of attention and executive function to examine functional connectivity of the ON and ECN attention networks in children and adolescents with PAE compared to unexposed controls. Based on previous fMRI findings (Fan et al., 2017; Little et al., 2018; O’Conaill et al., 2015; Santhanam et al., 2011), we hypothesized that relative to nonexposed controls, children and adolescents with PAE would show altered inter- and intranetwork functional connectivity among the ON and ECN, especially among long-range connections. Alterations in functional connectivity were expected to relate to attention and executive control performance in children with PAE.

2. Materials and methods

2.1. Participants

Participants (N = 77) between the ages of 6 and 18 (M = 13.01, SD = 2.77) years were recruited as part of a study of outcomes in FASD funded by the Kids Brain Health Network (KBHN; previously NeuroDevNet; Reynolds et al., 2011). Recruitment occurred at four research facilities in Canada: University of British Columbia, University of Manitoba, Queen’s University, and University of Alberta. Written informed consent was obtained from parents and/or legal guardians for all participants, and all procedures were approved by the local health research ethics committee for each study site. The current sample included the subset of participants from the KBHN with complete neuropsychological and neuroimaging data (Little et al., 2018; Long et al., 2019; Treit et al., 2016). 37 children with PAE were compared to 40 nonexposed typically developing controls in the current analyses. The current sample did not significantly differ from that of the overall study (n = 109) in terms of age (p = .716) or sex (p = .929).

Children with PAE were seen at local FASD clinics at each site, and were diagnosed according to the 2005 Canadian Guidelines for FASD diagnosis (Chudley et al., 2005). The diagnoses of the children with PAE are summarized in Table 1. All nonexposed controls were free of diagnosed neurodevelopmental disorders and PAE.

| Statistic | PAE Group (n = 37) | TD Controls (n = 40) | p |
|---|---|---|---|
| Age (M ± SD years) | 12.8 ± 2.8 | 13.2 ± 2.8 | .716 |
| Sex (% males) | 18 (49) | 15 (38) | .929 |
| Handedness (% right) | 29 (78) | 36 (90) | .001 |
| Ethnicity (%) | | | |
| First Nations | 11 (30) | 0 (0) | .001 |
| Asian | 0 (0) | 0 (0) | .001 |
| Caucasian | 13 (34) | 35 (87) | .001 |
| African American | 1 (3) | 0 (0) | .001 |
| Indian | 1 (3) | 0 (0) | .001 |
| Other | 11 (30) | 5 (13) | .001 |

Note. *Statistics for comparison between Caucasian not Caucasian. ARND: alcohol-related neurodevelopmental disorder; FAS: fetal alcohol syndrome; M = mean; SD = standard deviation.
2.2. Cognitive measures

Each participant completed a standardized neuropsychological assessment on the same day as the MRI scan. Assessments were performed by research assistants who were trained by a single neuropsychologist to ensure consistency across research sites. Cognitive results for the larger sample have been reported elsewhere (Little et al., 2018; Paolozza et al., 2014a, 2014b).

For the current study, select subtests from the Developmental Neuropsychological Assessment (NEPSY-II; Korkman et al., 2007) and the Behavior Rating Inventory of Executive Function (BRIEF) Parent Form (Gioia et al., 2000) were included as measures of attention and executive control. These subtests have strong psychometric properties, can generally distinguish children with PAE from controls, and are commonly used in clinical practice (Doyle et al., 2018; Korkman et al., 2007; Rasmussen et al., 2013). The BRIEF Parent Form is a questionnaire that assesses different functional domains pertaining to inhibition, cognitive flexibility (shift), and emotional control, cumulatively providing a Global Executive Composite score using standardized T-scores (i.e., $M = 50$, $SD = 10$; with scores > 65 indicating clinical impairment). It has strong psychometric properties, and has been used to study outcomes in PAE, among other neurodevelopmental disorders (Gioia et al., 2000; Nguyen et al., 2014).

2.3. Measures of functional connectivity

As previously described (Little et al., 2018; Long et al., 2018), all participants completed an MRI, including T1-weighted structural and rs-fMRI sequences, on the same day as the neuropsychological testing. The T1-weighted imaging acquisition used an axial MPRAGE with 160 slices, repetition time (TR) = 2100 ms, echo time (TE) = 3.5 ms, inversion time = 1100 ms, flip angle = 15°, and isotropic voxel size = 1 mm$^3$. The rs-fMRI acquisition parameters included 140 volumes with TR = 2500 ms, TE = 30 ms (TE = 40 ms at University of Alberta), axial slices = 40, flip angle = 90°, and isotropic voxel size = 3 mm$^3$. Participants were instructed to keep eyes closed and not think of anything particular during the rs-fMRI scan.

2.3.1. Image preprocessing

Data preprocessing was conducted on the rs-fMRI data, as previously described (Long et al., 2018). This included slice timing correction, head motion correction, nuisance signals regression (head motion, global signal and signals from cerebrospinal fluid and white matter), linear detrending, band-pass filtering (0.009–0.08 Hz), standard space transformation, and spatial smoothing using 4 mm$^3$ full-width at half-maximum (FWHM) of the Gaussian kernel, was done using Analysis of Functional NeuroImages and the FMRIB Software Library (Cox, 1996; Jenkinson et al., 2012). Volumes with relative frame displacement > 0.3 mm were excluded to control for motion artifacts.

2.3.2. Network construction

A region-of-interest (ROI) approach was used to define regions (nodes) of each attention network in accordance with published literature (Peterson and Posner, 2012). Selected ROIs for each network are summarized in Table 2 and shown in Fig. 1. ROIs were defined as the extracted time course within 6 mm of the center of the respective Montreal Neurological Institute (MNI) coordinates with no overlap (see Table 2 and Fig. 1). A connectivity matrix was subsequently constructed for each participant based on the temporal correlation coefficient across ROI pairs (i.e., edges), which were then transformed to Fisher’s z scores in AFNI (Cox, 1996).

| ROI | MNI coordinates* |
|-----|------------------|
| L dACC | −1 10 46 |
| L Precuneus | −9 −72 37 |
| L Thalamus | −12 −15 7 |
| L aPFC | −28 51 15 |
| L mCC | 0 −29 30 |
| L dFC | −41 3 36 |
| L dIPFC | −43 22 34 |
| L aL/RO | −35 14 5 |
| R Precuneus | 10 −69 39 |
| R Thalamus | 10 −15 8 |
| R aPFC | 27 −50 23 |
| R dFC | 41 3 36 |
| R dIPFC | 43 22 34 |
| R aL/RO | 36 16 4 |
| L TPJ | −53 −46 17 |
| L FEF | −25 −12 55 |
| L VFC | −42 20 6 |
| R TPJ | 53 −46 17 |
| R FEF | 24 −13 51 |
| R VFC | 42 20 6 |
| L IPS | −31 −59 42 |
| L IPL | −51 −51 36 |
| R IPS | 30 −61 39 |
| R IPL | 51 −47 42 |

Note. *Coordinates reported in standard space. ECN = executive control network; ON = orienting network; L = left hemisphere; R = right hemisphere; dACC = dorsal anterior cingulate cortex; aPFC = anterior prefrontal cortex; mCC = medial cingulate cortex; dFC = dorsal frontal cortex; dIPFC = dorsal lateral prefrontal cortex; aL/RO = anterior insula/fronatal operculum; IPS = intraparietal sulcus; IPL = intraparietal lobe; TPJ = tempoperioral junction; FEF = frontal eye fields; VFC = ventral frontal cortex.

2.3.3. Functional connectome

Averaged graph-theory based metrics were calculated on the weighted network, excluding any negative correlations. The following metrics were calculated: clustering coefficient (the connectivity status of each of the region’s neighbors); shortest path length (the shortest pathway that connects each pair of regions); local efficiency (the efficiency of information transfer between each ROI and its neighbors); global efficiency (the efficiency of information transfer between each ROI and other network regions); and degree centrality (the number of edges connect to each region). These metrics are defined elsewhere (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009).

2.4. Analytic approach

Group demographics were compared using $\chi^2$ and t-tests for categorical and continuous variables, respectively (Table 1). Group comparisons between the children with PAE and the nonexposed controls were performed for the functional connectivity between all pairs of regions using permutation testing at a statistical threshold of $p < 0.01$ to control for multiple comparisons. Groups were then compared on the averaged functional connectivity between the regions within the ON to the regions within the ECN to examine network-to-network differences using permutation testing at a statistical threshold of $p < 0.05$. For the structural connectome metrics, permutation-based group comparisons were conducted in the GRETNA toolbox to examine the included graph theoretical metrics (e.g., global efficiency; Wang et al., 2015). For all analyses, age, sex, handedness, average frame-wise displacement from motion correction, and research site were included as covariates. The results were displayed by BrainNet Viewer (Xia et al., 2013) and circularGraph v2.0.0.0 (Paul Kassemah 2020, freely available at https://www.github.com/paul-kassemah-math works/circularGraph). Analyses were conducted for the functional connectivity among all ROI pairs (i.e., region-based functional
connectivity) and for the averaged functional connectivity among regions within the ON and ECN (network-based functional connectivity), although only the results that significantly differed between the groups are reported below in the interest of space.

To determine whether cognitive performance differed between the children with PAE and controls and was related to functional connectivity metrics, multiple multivariable linear regressions were used to determine whether there was an effect of predictors group and functional connectivity and their interaction with covariates sex and handedness. The interactions between functional connectivity metrics and group are reported for the models that reached statistical significance at a threshold of $p < .05$.

3. Results

3.1. Cognitive function

As summarized in Table 3, children with PAE performed significantly worse on most cognitive measures relative to the TD controls.

3.2. Baseline functional connectivity

For the functional connectivity network analysis, a one-sample $t$-test was performed on the connectivity matrices of participants to check baseline network structure within each group separately using a threshold of $p < .01$. The baseline functional connectivity for each group is shown in Fig. 2.

3.3. Functional connectivity and relation to cognitive performance

3.3.1. Region-based functional connectivity

Children with PAE and the TD controls differed significantly in the functional connectivity of several ROI pairs of both the ON and ECN attention networks (see Table 4). As shown in Fig. 3a, the direction of the group differences varied by region. There was an overall pattern of lower functional connectivity in long-range connections among anterior and posterior regions (e.g., left temporoparietal junction with the left ventral frontal cortex and anterior insula/frontal operculum; left intraparietal sulcus and bilateral anterior insula/frontal operculum) and higher connectivity in shorter connections among regions within the frontal (i.e., left anterior prefrontal cortex with the left thalamus, anterior insula/frontal operculum, and ventral frontal cortex) and parietal (i.e., right precuneus with bilateral intraparietal lobe) lobes in the group with PAE as compared to the TD controls. The functional connectivity of several edges that differed between groups was significantly associated with cognitive performance (see Fig. 3b).

As shown in Fig. 4 and summarized in Table 5, group differences in cognitive scores were moderated by functional connectivity of several attention network ROI pairs (edges). For the group with PAE, NEPSY-II Inhibition-Inhibition and Inhibition-Switching performance was significantly negatively associated with functional connectivity between the left anterior insula/frontal operculum and left intraparietal sulcus. For the TD controls, BRIEF inhibition was significantly positively associated with functional connectivity between the left anterior insula/frontal operculum and right anterior prefrontal cortex.

3.3.2. Network-based functional connectivity

As illustrated in Figs. 5 and 6, the average functional connectivity of the ON and ECN, and the difference between those networks did not differ significantly between the groups (ON: $t = -0.68, p = .502$; ECN: $t = -0.98, p = .329$; ON-ECN: $t = -0.95, p = .345$), but was significantly associated with and moderated group differences in cognitive performance (see Table 6). For the group with PAE, average functional connectivity of the ON and ECN was significantly associated with NEPSY-II Animal Sorting (negatively) and BRIEF-Inhibition and Global Executive Composite scores (positively), respectively. For the TD control group, average functional connectivity of the ECN was significantly positively associated with NEPSY-II Inhibition-Inhibition scores. As illustrated in Fig. 6b, the difference in average functional connectivity between the ON and ECN was significantly associated with NEPSY-II Inhibition-Inhibition scores, but differently in the group with PAE (negatively) as compared to the controls (positively).
3.4. Functional connectome

There were no significant group differences in any of the examined graph-theoretical network metrics (global efficiency, local efficiency, clustering coefficient, shortest path length, and degree centrality).

4. Discussion

Here we show disrupted functional connectivity in attention networks in children and adolescents with PAE. Furthermore, these disruptions were related to cognitive performance, suggesting that this altered connectivity may be an indication of neural inefficiency underlying reduced attention network specialization following PAE. Attention difficulties are common in individuals with PAE (see review by Mattson et al., 2019). However, impairments are not typically global, but rather occur in discrete domains of attention, and the neural mechanisms underlying these deficits have remained unclear in FASD. This study investigated the neural correlates of attention in children and adolescents with histories of PAE and nonexposed controls.

There was an overall pattern observed both within and between the attention networks whereby functional connectivity was reduced in longer anterior-posterior pathways and increased in shorter posterior-posterior and anterior-anterior pathways for children with PAE relative to controls. Children with PAE showed reduced connectivity within the ventral attention system (i.e., the temporoparietal junction and ventral frontal cortex) of the ON, which is implicated in bottom-up reorienting in response to perceived stimuli. Children with PAE also showed reduced connectivity between parietal regions of both the dorsal and ventral subnetworks of the ON and the anterior insula/frontal operculum of the cingulo-opercular subnetwork of the ECN. In contrast, the connectivity between more proximally located prefrontal cortical regions, and regions within the frontoparietal control (i.e., precuneus-intraparietal lobe) or cingulo-opercular (i.e., anterior prefrontal cortex-thalamus and -anterior insula/frontal operculum) subnetworks of the ECN was greater in children with PAE as compared to nonexposed controls. When considering the evidence of distinct sub-networks within both the ON (dorsal and ventral attention system) and the ECN (frontoparietal control system and cingulo-opercular system; detailed review provided in (Peterson and Posner, 2012), these findings suggest that PAE differentially disrupts the efficiency of information processing between as compared to within discrete attention networks. This corroborates...
Fig. 3. Significant group-level differences ($p < .01$) in the functional connectivity of ROI pairs (edges) between the children with prenatal alcohol exposure (PAE) and TD controls are shown in the left graph, and the significant group differences in both region-to-region functional connectivity and its relation to cognitive measures (see Fig. 4) are shown on the right. Blue lines indicate PAE < control and red lines indicate PAE > control for functional connectivity; line thickness represents the (absolute) mean difference between the groups in functional connectivity, with greater thickness indicative of larger group-level differences. Abbreviations defined in Table 2.

Fig. 4. Scatterplots illustrating the group by functional connectivity interactions that were significant ($p < .05$) for cognitive scores. Graphs show the within-group correlations between the functional connectivity of attention network ROI pairs and standard scores on (a) performance-based measures and (b) parent ratings of children’s attention and executive control. Note that lower NEPSY-II and higher BRIEF scores are indicative of greater impairment. Abbreviations defined in Table 2.
previous findings of reduced long-range, internetwork and increased localized, intra-network connectivity among brain regions involved in other neural networks (e.g., default mode network) in children and adolescents with PAE (Fan et al., 2017; Little et al., 2018; O’Conaill et al., 2015; Santhanam et al., 2011; Wozniak et al., 2017). This is, however, the first study to specifically examine the functional connectivity among regions of distinct attention networks.

Reduced functional connectivity could potentially reflect more diffuse recruitment of distributed brain regions and functional networks in children with PAE. Greater connectivity within the ECN (frontoparietal and cingulo-opercular systems) could also indicate inefficient neural function. However, the neurological basis for the observed alterations in functional connectivity are not clear, and likely involves a complex and dynamic interplay between the brain tissue malformations.

### Table 5

| Cognitive Measure       | ROI Pair Functional Connectivity | Group       | Group x Functional Connectivity |
|-------------------------|----------------------------------|-------------|--------------------------------|
|                         |                                  | PAE Group   | TD Controls                    | p      |
|                         |                                  | r           | p                             | r      | p |
| NEPSY-II Subtests       |                                  |             |                                |        |
| Inhibition-Naming       | R IPL-R Precuneus                | –0.32       | 0.064                         | 0.27   | 0.096 | 0.20 |
| Inhibition-Inhibition   | L IPS-L aI/fO                     | –0.37       | 0.027                         | 0.28   | 0.087 | 0.15 |
| Inhibition-Switching    | L IPS-L aI/fO                     | –0.53       | 0.001                         | 0.11   | 0.503 | 0.008 |
| BRIEF Parent Form       |                                  |             |                                |        |
| Inhibition              | R aPFC-L aI/fO                    | –0.23       | 0.186                         | 0.48   | 0.002 | 0.004 |

Fig. 5. The a) average functional connectivity (FC) of the ON and ECN of attention and b) its relation to cognitive scores for each group. Red line/dots = the PAE group; blue line/dots = the TD control group. Note that lower NEPSY-II and higher BRIEF scores are indicative of greater impairment.
and altered neurodevelopment trajectories that can occur following PAE (Lebel et al., 2012). One study reported decreased functional connectivity in the right temporoparietal junction and altered microstructure of underlying white matter pathways in children with PAE, suggesting that these may be related (O’Conaill et al., 2015). However, this has not been directly examined and warrants further investigation. Neuro-developmental stage and trajectory must also be considered, given that there is evidence of critical periods of microstructural development, during which neurons may increase complex executive processing abilities, especially those related to social adaption, theory of mind, and executive control (reviewed in Peterson and Posner, 2012).

As expected, functional connectivity was associated with and moderated some of the group-level differences in cognitive performance and parent ratings (Little et al., 2018; O’Conaill et al., 2015). The children with PAE who showed more similar functional connectivity to controls tended to have better attention and executive control abilities. Reduced functional connectivity between the temporoparietal junction and the ventral frontal cortex suggests that PAE may disrupt the ventral attention system, which is associated with bottom-up information processing. Indeed, performance on executive control tasks was inversely associated with functional connectivity between the left anterior insula/frontal operculum and left intraparietal sulcus. This suggests that the attention networks may not be as discrete or specialized in children with PAE. While the average connectivity of the ON and ECN was similar between groups, cognitive performance during an inhibition task was worse and differentially related to functional connectivity in PAE relative to the TD controls, suggesting that relatively proportional increases or decreases of inter- as opposed to intranetwork connectivity among the regions of the ON and ECN may not be advantageous in PAE (as it is in the unexposed controls). This, in turn, could lead to the recruitment of more diffuse brain regions and inefficient functional connectivity between the ON and ECN. Findings also may offer a potential explanation as to why common medical interventions with high efficacy for the treatment of attention difficulties in unexposed children with ADHD are not as effective in children with PAE (Peadon et al., 2017).

There are some limitations of the current study. As is the case with nearly all studies of PAE, the timing and extent of PAE for the current sample was not always known, though PAE was confirmed in all cases. Moreover, children with PAE also may have exposure histories that include other known teratogens, including nicotine.

### 4.1 Conclusions

Reduced internetwork and increased intranetwork connectivity were observed in children with PAE as compared to controls, and were associated with cognition. The overall pattern of results provides further support for reduced attention network specialization and inefficiency following PAE. Findings have important scientific and clinical implications for understanding deficits and implementing interventions that target attention deficits in children with FASD. Future examinations of the underlying structure of the attention networks (e.g., using diffusion...
MRI) could be beneficial in understanding the biological bases of the observed alterations in functional connectivity. Greater research into the functional brain differences that occur during complex attention and inhibitory control could also be informative (e.g., task-based/event-related MRI or EEG) in elucidating specific biomarkers for complex attention and executive control deficits in children with PAE.

Data statement

Data are not publicly available in order to protect the privacy of participants, but could be made available upon reasonable request to the corresponding author.

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Declaration of Competing Interest

The authors report no declarations of interest.

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