Changes in resting-state functional connectivity in children with fetal alcohol spectrum disorders

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INTRODUCTION

- Resting state fMRI (rs-fMRI) is used to identify brain regions that are temporally correlated when the subject is not performing any explicit task [1].
- To date, rs-fMRI has been examined in fetal alcohol spectrum disorders (FASD) in only one child [2-4] and one adult [5] sample. Moreover, none of these studies used independent component analysis (ICA) to examine multiple resting state networks (RSNs), and the adult study examined only the default mode network (DMN).
- This pediatric study is the first to use ICA-based dual regression [6] to quantitatively assess the effects of prenatal alcohol exposure on multiple RSNs and the first to examine effects on RSNs in relation to prospectively-ascertained continuous measures of fetal alcohol exposure.

METHODOLOGY

- Participants: 57 right-handed children (mean±sd age: 11.3±0.9 yr) from the Cape Town Longitudinal Cohort study [7]: 19 with full or partial fetal alcohol syndrome (FAS/PFAS); 19 non-syndromal heavily exposed (HE); 19 non- or minimally-exposed controls (Ctl).
- Record of maternal alcohol consumption: Timeline follow-back interviews [8] were conducted with the mothers to record their alcohol consumption. Two interviews were administered during pregnancy and one at 1 month postpartum.
- FASD group: Mothers of children in the FAS/PFAS and HE groups consumed an average of 7.4 drinks/occasion on 1.4 days/week during pregnancy. Control group: All of the Ctl mothers abstained from drinking except for 1 who drank 1 drink 4 times during pregnancy.
- FASD diagnosis: All of the children were evaluated for FAS facial dysmorphology and growth at 5 years of age by two expert U.S. FAS dysmorphologists following the revised Institute of Medicine criteria [9].
- Scanning protocol: Scans were performed on a 3T Allegra MRI (Siemens, Erlangen, Germany). 180 T2* weighted volumes were acquired while subjects lay at rest using a gradient echo EPI (TR 2000ms, TE 30ms, 3.1x3.1x3mm^3, 34 slices). T1-weighted structural images were acquired using a 3D EPI-navigated multiecho MPRAGE sequence (resolution=1.3x1.0x1.3mm^3, FOV=167x256x256 mm^3, 128 slices, TR 2530 ms, TI 1100ms, TEs 1.53/3.21/4.89/6.57 ms, flip angle 7°) [10].
- Pre-processing: Preprocessing was conducted using afni_proc.py in AFNI and included the following standard procedures: motion correction, realignment, regression and blurring. All images were registered to a 3x3x3 mm^3 Talairach-Tournoux (TT) standard space.
- Analyses: Group ICA and dual regression were performed in FSL. Nine standard resting state networks (RSNs) were identified from 20 group components, and FSL-randomise was used to find significant clusters within each RSN (p<0.01, corrected for 9 networks) [11]. Values for mean fractional amplitude of low-frequency fluctuations (fALFF) were obtained in each cluster and correlated with a continuous measure of prenatal alcohol exposure, namely oz absolute alcohol consumed per day across pregnancy (AA/day; 1 AA/day≈2 standard drinks).

RESULTS

- Regions showing significant reductions (p<0.01, corrected for 9 networks) in resting state functional connectivity (RSFC) were found in 5 regions within 5 networks in children with FAS or PFAS (FAS/PFAS) compared to Ctls (Fig 1). Cluster size, peak coordinate and location of each ROI is shown in Table 1. In all 5 regions, increased alcohol exposure was associated with reduced RSFC (Table 1).

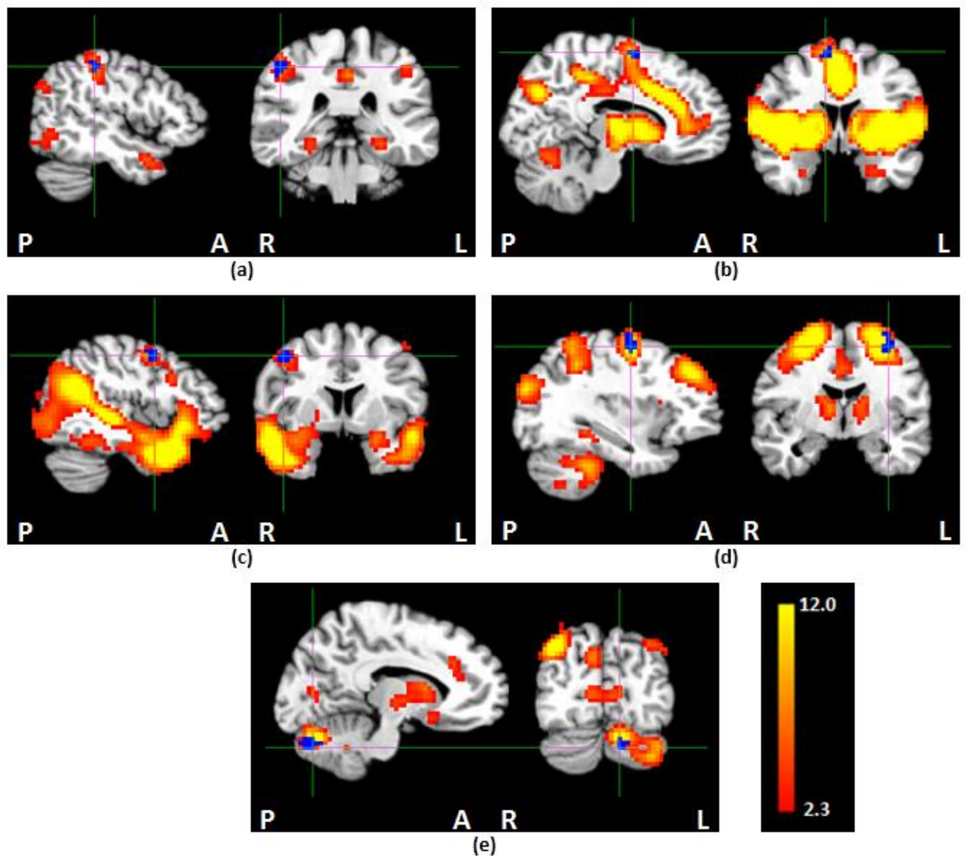

Figure 1. **Each panel shows the group ICA map of a resting state network thresholded at z>2.3 (hot colors) and clusters where children with FAS/PFAS had lower connectivity than controls (in blue; cross-hairs indicate the peak coordinates). (a) right (R-) postcentral gyrus within the DMN, (b) R-middle frontal gyrus within the salience network, (c) R-precentral gyrus within the ventral attention network, (d) left (L-) precentral gyrus within the dorsal attention network, and (e) L-crus II within the R-executive control network.**

Table 1. **Cluster sizes and peak coordinates (in TT standard space) of regions where children with FAS/PFAS have lower RSFC than controls. Also shown are correlations of mean fALFF in these ROIs with AA/day.**

Networks	Size (mm^3)	Peak coordinates (mm)			Locations	r (AA/day)
		X	Y	Z		
DMN	540	46.5	-31.5	44.5	R-postcentral gyrus	-0.46**
salience	351	10.5	-1.5	59.5	R-middle frontal gyrus	-0.54**
ventral attention	729	43.5	-7.5	44.5	R-precentral gyrus	-0.27*
dorsal attention	486	-31.5	-7.5	53.5	L-precentral gyrus	-0.29*
R-executive control	675	-10.5	-73.5	-30.5	L-crus II	-0.23†

†p<0.10, *p<0.05, **p<0.01.

- Additionally, non-syndromal HE children displayed lower functional connectivity in 3 of these regions, namely the R-postcentral gyrus of the DMN, R-middle frontal gyrus of the salience network, and R-precentral gyrus of the ventral attention network (panels 'a', 'b 'and 'c 'of Fig. 1, respectively).

DISCUSSION AND CONCLUSIONS

- The reduced connectivity found in the default mode network due to prenatal alcohol exposure (PAE) in this study is consistent with results of a previous study in adults [5].
- Significant correlations between mean RSFC and extent of prenatal alcohol exposure suggest dose-dependent impairment in these regions.
- The compromised RSFC we found in the DMN, ventral attention, and right executive control networks could be related to white matter deficits in the right superior longitudinal fasciculus, right corticospinal tract and left middle cerebellar peduncle, respectively, which have been seen in our previous DTI studies within this and other prenatal alcohol-exposed cohorts [12] and provide intra-RSN connections (Fig 2). This hypothesized relation to white matter impairment needs to be confirmed using additional tractographic analyses.

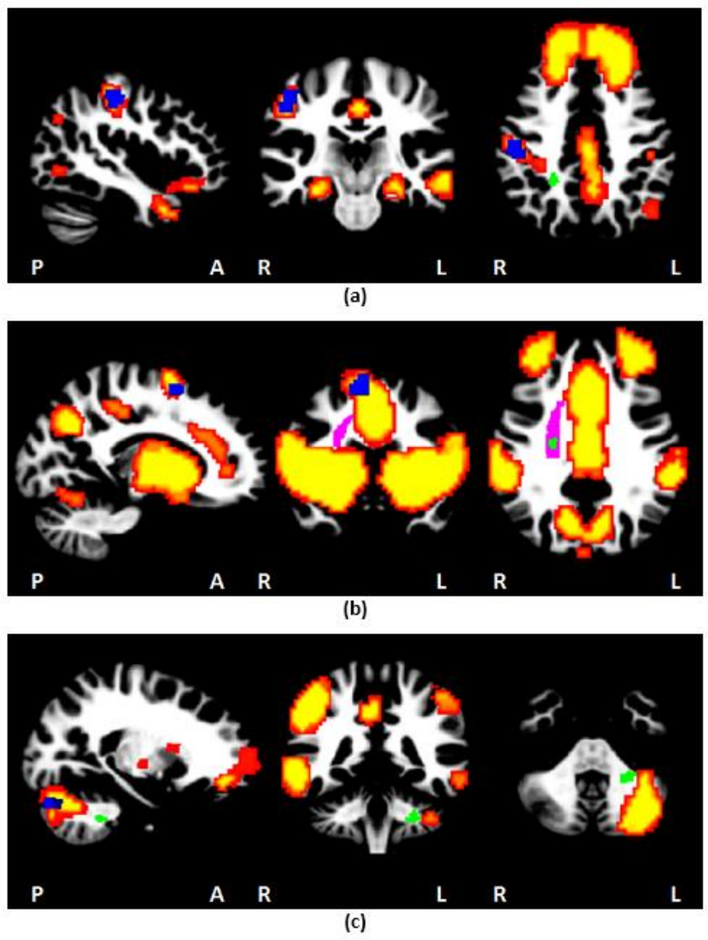

Figure 2. **Regions of functional connectivity differences (in blue) and WM alterations in intra-network tracts (in green), overlayed on thresholded rs-fMRI networks (hot colors). (a) The R-superior longitudinal fasciculus connects regions of the DMN; (b) the R-corticospinal tract, part of R-superior corona radiata (purple, JHU WM template from FSL), connects regions of the salience network; (c) the L-middle cerebellar peduncle connects regions of the R-executive control network.**

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