Altered Resting-State Default Mode Network Connectivity in Adults Prenatally Exposed to Alcohol

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Introduction

The recently characterized default mode network (DMN), described as consistent regions of higher activation during rest than during cognition [1], has been found to be altered in the resting state in several clinical populations [2,3]. Additionally, DMN deactivation during cognitive demand has been shown to be impaired in a subset of clinical conditions due to an inability to redistribute mental resources [4,5]. While prenatal alcohol exposure (PAE) is known to result in structural and functional brain damage, DMN activity has not been previously examined in the PAE population.

Methods

Image Acquisition: All scans were performed on a 3T Siemens Trio scanner. Both scans were single-shot T2*-weighted EPI sequences, with the following parameters: resting state (10 contiguous axial slices, 5 mm thickness, TR/TE/FA/FOV 750ms/34ms/50°/22cm, scan time of 3:34 min, 280 time points) and functional run (34 contiguous axial slices, 3 mm thickness, TR/TE/FA/FOV of 3000ms/32ms/90º/22cm, scan time of 5:06 min, 102 time points). ***Experimental design:*** PAE and healthy control subjects between 19-23 years old were recruited for the study from a longitudinal cohort. PAE subjects were characterized as prenatally exposed to alcohol based on repeated physical examination for growth retardation and dysmorphia, IQ testing, and by screening of the maternal population for alcohol use [6]. Participants were divided into three groups: 1) PAE, positive for dysmorphia (n=19 for both scans); 2) PAE, non-dysmorphic (n=22 for both scans); 3) socio-economic status matched controls (n=21 for resting, n=19 for functional). All participants gave written consent. In the resting state run, participants were simply asked to gaze at a fixation cross. For the functional run, subjects were asked to perform alternating letter-matching and subtraction tasks in block-design [7]. The letter task required subjects to match a letter at the top of the presentation screen with one of two other letters displayed at the bottom using a button response box. The subtraction task asked subjects to subtract a number at the top of the screen from 11 and similarly choose the correct answer from one of two numbers at the bottom of the screen. ***fMRI Data Analysis***: Preprocessing in AFNI (http://afni.nimh.nih.gov) included: slice timing correction, volume registration, band pass filtering (resting data only), signal normalization (functional data only), 5mm FWHM Gaussian blur, and whole brain signal subtraction (resting data only) [8]. An activation map of arithmetic task vs letter-matching task was rendered using GLM analysis. Regions of deactivation in this map were then identified, namely anterior and posterior cingulates (ACC and PCC). Resting state analysis was done by projecting the PC region from the deactivation map back into native space for each subject for identification of seed region. Cross-correlation analysis was performed on time courses, with the deactivated PCC region as the seed. Correlation coefficients (converted to z-score) were compared between control and PAE groups by t-test. For arithmetic task, regression coefficients (proportional to percent signal change) were also averaged over ACC deactivation region in native space and compared between groups by t-test.

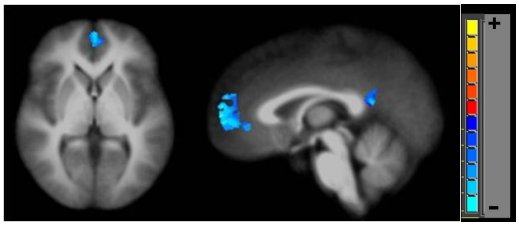

Figure 1: Activation map showing regions of deactivation during arithmetic task vs control task for all three groups. Regions of interest are anterior and posterior cingulates. Threshold was p<0.05 with a minimum cluster of 100 ul.

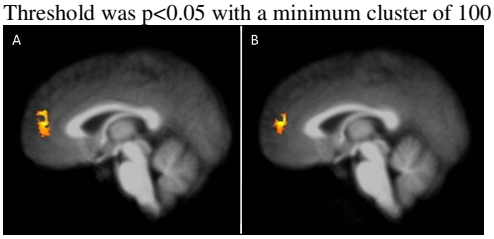

Figure 2: Subtraction maps of resting state connectivity in anterior cingulate for A) Control-Non dysmorphic PAE and B) Control-Dysmorphic PAE. Threshold was p<0.05 with a minimum cluster of 300 ul.

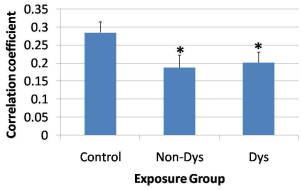

Figure 3: Resting state correlation of ACC target region with PCC seed region. *=significantly different from control group. Error bars represent standard error.

Results

Figure 1 indicates regions of deactivation during the arithmetic task, as compared to the control task. The PCC was used as the seed and the ACC as the target for the resting state analysis. Figure 2 shows subtraction maps comparing resting connectivity with the PCC between control and exposed groups. Control subjects had significantly greater connectivity than both non-dysmorphic and dysmorphic PAE groups. Correlation coefficients of voxels in individual ACC regions were also significantly greater in the control group as compared to PAE groups (Figure 3; p=0.019 and p=0.027 for non-dysmorphic and dysmorphic, respectively). In contrast, deactivation during the arithmetic task, as measured by regression coefficient in the ACC region was not significantly different from the control subjects (p=0.26 and p=0.18 for non-dysmorphic and dysmorphic groups, respectively).

Conclusion

Resting state synchronous activity in the DMN was found to be decreased in both the non-dysmorphic and dysmorphic PAE groups as compared to healthy control subjects. Given known structural alteration of the corpus callosum due to PAE [9], it is possible that the reduced DMN connectivity is a product of reduced structural white matter connectivity between the ACC and PCC. In contrast, the cognitive task-driven DMN deactivation was not significantly different between groups. Since DMN deactivation is an indicator of task-related arousal [10], results imply that while PAE-induced damage may affect baseline arousal, it does not impair arousal during cognition. This in turn implies that the diminished task performance and accompanying brain activation observed during the arithmetic task (results to appear elsewhere) is the result of cognitive deficiency and not task-related arousal in PAE individuals. The present study provides more evidence of functional deficits and specifically of cognitive impairment caused by PAE.

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