Subgenual anterior cingulate connectivity in school age children with a history of Preschool-Onset Major Depressive Disorder: An fcMRI study

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Introduction: Multiple neuroimaging studies have pointed to the importance of the subgenual anterior cingulate cortex (sgACC) in the modulation of emotional behaviors. This importance has been further underscored by atypical findings of both its structure and function in mood disorders such as depression. Recent research has also pointed to altered functional connectivity between the sgACC and other brain regions when 'default-mode' and 'affective' networks were examined in depression. These findings of atypical connectivity in depression are of particular importance as they begin to place previously identified focal abnormalities within the context of disordered neural systems. However, there is still very little understanding of the *development* of these disordered neural systems and their potential importance for understanding symptom onset and identifying more specific targets for early intervention. As such, the current study sought to begin addressing this question using a unique sample of school age children participating in a longitudinal study of Preschool-Onset Major Depressive Disorder (PO-MDD; see Luby et al., 2009, Arch Gen Psych). Given the noted importance of the sgACC in modulating emotional behaviors and its relevance to depression, this region was selected as an a priori seed region of interest for resting-state fMRI analyses to examine potential depression-related connectivity differences.

Methods: 32 children with no history of head trauma, neurological disease, or developmental delay participated in the current study. Children were placed into groups based upon the presence/absence of PO-MDD. PO-MDD was defined by meeting all DSM-IV MDD symptom criteria (although not required to meet 2 week duration criterion) prior to age 6 according to the Preschool Age Psychiatric Assessment interview. This resulted in a group of 17 PO-MDD children (6M; mean age 9.6 [±.93] years) and 15 healthy controls (7M; mean age 9.5 [±1] years). Prior to their scan, children completed the Child Depression Inventory and the Children's Sadness Management Scale. Groups were medication naive and did not differ in age, gender, or current level of depressive symptomatology (all $p > .05$). The Institutional Review Board at Washington University in St. Louis approved all experimental procedures. Imaging data were collected using a 3T TIM TRIO Siemens whole body system. The image acquisition included a T1 [sagittal acquisition, TE=2.9ms, TR=6.6ms, flip angle=8°, 1 acquisition, 128 slices, 1x1x1 mm voxels] image and functional images collected with a 12-channel head coil using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (TR=2500ms, TE=27ms, FOV=256mm, flip=90°). During each functional run, sets of 36 contiguous axial images with isotropic voxels (4mm^3) were acquired parallel to the anterior-posterior commissure plane. Two functional runs of 128 TRs were collected while children rested silently with their eyes closed. Prior to preprocessing, the first 5 frames of each run were discarded to allow for signal stabilization. Data were reconstructed into images and normalized across runs by scaling whole-brain signal intensity to a fixed value and removing the linear slope to counteract effects of drift. MR data was then corrected for head motion using rigid-body rotation and translation correction algorithms. Following motion correction, the functional images were registered to Talairach space using a 12 parameter linear (affine) transformation and smoothed with a 6mm FWHM Gaussian filter. Several additional pre-processing steps including temporal filtering retaining frequencies in the 0.009-0.08 Hz band and removal by regression of several sources of spurious variance were carried out as well. The coordinates x=±4 y=22 z=-5 were used to create 6 mm spheres centered in the sgACC for each hemisphere (coordinates adopted from Kelly et al., 2009, Cereb Cortex). Correlation maps for each subject were produced for each seed by extracting their BOLD time course and computing the correlation coefficient between these time courses and those from all other brain voxels. Fisher's r to z transform was applied to the individual correlation maps, and group comparisons were conducted with this transformed data using a random effects analysis. Resulting t values were converted to Z scores and used in combination with cluster size to yield a corrected false positive rate of .05 (uncorrected p-value [<.0001]+cluster size thresholding [13 voxels]).

Figure 1: Group Connectivity Differences
Blue = Con>PO-MDD; Red = PO-MDD>Con

Results and Discussion: Using an a priori identified seed region in the sgACC, significant differences in patterns of connectivity were found between the PO-MDD and healthy children in both the right and left hemispheres. Specifically, the right sgACC in the healthy comparison group was found to have greater connectivity with the dorsal anterior cingulate (BA32), medial frontal gyrus (BA 10), caudate, claustrum, and dorsal medial prefrontal regions (DMPFC; BAs 8,9). Conversely, children with a history of PO-MDD demonstrated an increased pattern of connectivity between the right sgACC and the inferior frontal gyrus (BA 47) and thalamus (see figure 1A). When the left sgACC was examined, the healthy comparison group demonstrated increased connectivity between this region and the medial prefrontal gyrus (BA 10) and putamen while children with a history of PO-MDD exhibited increased connectivity with the periaqueductal gray, precuneus (BA 7), and paracentral lobule (BA 5; see figure 1B). Post hoc examinations revealed a negative relationship between right sgACC-right DMPFC (BA 8) connectivity and current level of emotional dysregulation (i.e, decreased connectivity/increased dysregulation; pearson $r = -.523$, $p = .002$ [2-tailed]). Further, right sgACC-right DMPFC connectivity scores were found to significantly predict ($B = -6.4$, $SE = 2.7$, $p = .028$) as well as explain a significant proportion of variance in emotional dysregulation scores ($R^2 = .167$, $F(1,21) = 5.54$, $p = .028$) even after current age, gender, history of internalizing/externalizing disorder, and negative affect at time of scan were controlled for. When considered as a whole, the results suggest a pattern of atypical connectivity between the sgACC and cortical and subcortical regions generally associated with cognitive control (decreased) and visceromotor/self-focused (increased) operations in children with a history of PO-MDD. Further, they suggest a clinically relevant 'brain-behavior' relationship between atypical functional connectivity of the right sgACC-right DMPFC (BA 8) and disruptions in emotional behavior.

Conclusions: The current findings are in line with a growing body of literature suggesting atypical patterns of functional connectivity in depression. In addition, it extends this literature by demonstrating that disruptions are present even in school age children with a history of PO-MDD suggesting these brain changes are associated with a very early episode of MDD. Further research is needed to clarify the current findings of atypical sgACC connectivity as a precursor to or consequence of PO-MDD.