

## Increased local connectivity in children with ADHD

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**Background & Introduction:** Functional connectivity is defined as inter-regional synchrony of low-frequency fluctuations in blood oxygenation level dependent (BOLD) functional MRI data. Differences in resting functional connectivity have been reported for several neuro-developmental disabilities in both children<sup>2</sup> and adults<sup>3</sup>. Attention-deficit Hyperactivity Disorder (ADHD) is a highly prevalent developmental disorder characterized by impairments in attention, impulse control and hyperactivity. During fast reaction time tasks, children with ADHD show high rate of commission errors and high variability in reaction time<sup>4</sup>. Poor performance in these tasks has been related to deficits in motor response inhibition and attentional lapses, two major ADHD symptoms. The pre-supplementary motor area (pre-SMA) is considered a key region involved in motor response inhibition<sup>4</sup>, and functional abnormalities in this area have been reported in children with ADHD<sup>5,6</sup>. However, to our knowledge, there have been no reports investigating the functional connectivity of this area in ADHD. Although the functional role of the default mode network (DMN) is still controversial, previous findings in ADHD suggest that the attentional deficits may be related to abnormalities in the DMN. Differences in DMN connectivity have been previously reported in adults with ADHD. In this study comparing children with ADHD to age-matched neurotypical children, we report differences in functional connectivity of the pre-SMA and the DMN.

**Methods - Data Acquisition:** Informed consent was obtained from parents of typically developing (TD) children (n=28; aged 8 through 12) and children diagnosed with ADHD (n=16; aged 8 through 12) to participate in an IRB approved study; the children gave verbal assent. Scans were obtained at 3 T (Philips HealthCare) with an 8-channel head coil, using SENSE-EPI with TR/TE = 2500/30 ms, flip-angle 70°, 2.67 mm x 2.67 mm x 3 mm nominal voxel size with a 1 mm slice gap. During the 5 minute 20 second BOLD fMRI scan, participants were instructed to relax and to fixate on a cross-hair. An MP-RAGE anatomical scan (1 mm x 1 mm x 1 mm nominal voxel size) was also obtained from each participant. The revised Physical and Neurological Assessment for Subtle Signs (PANESS<sup>7</sup>), an assessment of motor function in children, was also administered to each participant.

**Methods - Data Analysis:** fMRI data were slice time corrected, realigned, normalized to MNI space using unified segmentation and smoothed using a Gaussian kernel of FWHM 8 mm using SPM 5. Data were then band-pass filtered with pass-band 0.01 to 0.1 Hz. Realignment parameters, global signal, and nuisance covariates from white-matter and cerebro-spinal fluid extracted using COMPCOR<sup>8</sup>, were regressed out from the data. Functional connectivity of the pre-supplementary motor area (pre-SMA) and the precuneus (a key locus of the default-mode network) was computed using Pearson's correlation, and converted to Z-scores using the Fisher transform. Connectivity differences between groups were computed using random-effects analysis of the connectivity Z-score; significance was corrected for multiple comparisons using false discovery rate to obtain an effective  $p < 0.05$ .

**Results:** The left pre-SMA was significantly more connected to the right pre-SMA and to the right primary motor cortex in children with ADHD than in TD children (Figure 1 panel a). The precuneus (part of the DMN) was significantly more connected to the posterior cingulate cortex in children with ADHD than in TD children (Figure 1 panel b). In children with ADHD, but not in typically developing children, the connectivity of the pre-SMA to the bilateral superior temporal gyrus (Brodmann Area 42) was significantly correlated with higher (more impaired) PANESS score (Figure 1 panel c).

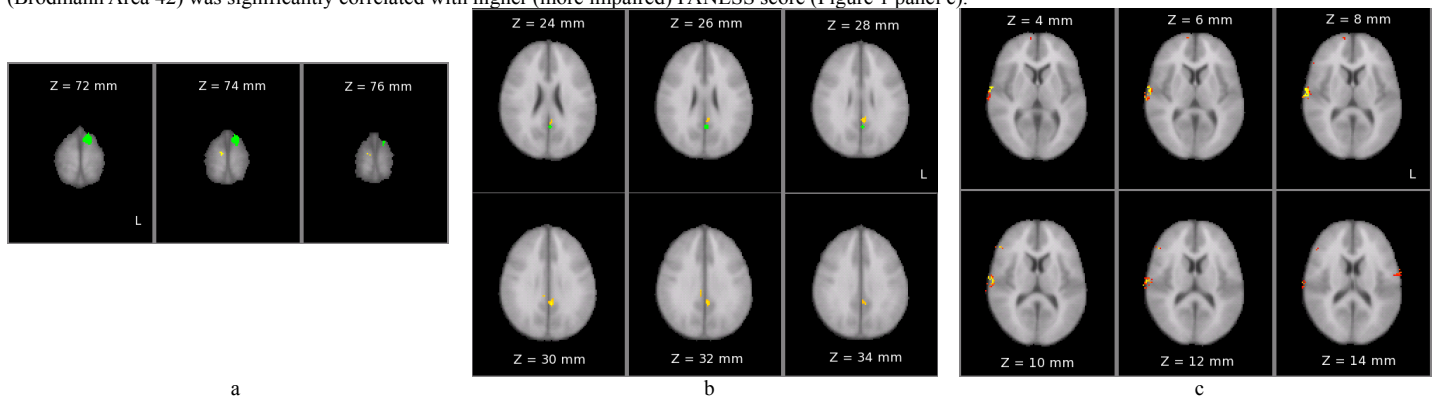


Figure 1. Panel a depicts the contrast of left pre-SMA (green) connectivity between children with ADHD and typically developing children. Panel b depicts the contrast of precuneus (green) connectivity between children with ADHD and typically developing children. Panel c are regions whose connectivity to the pre-SMA (green blob in panel a) is significantly correlated with higher (more impaired) PANESS score.

**Discussion and Conclusions:** To our knowledge, this is the first report of differences in functional connectivity in children with ADHD. In prior studies, children with ADHD have been shown to have atypical pre-SMA activity<sup>4</sup>. Here we observe increased local resting connectivity of the motor cortex in children with ADHD. Medial premotor regions, including the SMA, appear to be critical to maintaining motor persistence; given the “task demand” of lying still during resting state, increased SMA-motor cortex connectivity in ADHD may be due to increased involvement of this circuit to maintain “rest”. Also, children with ADHD who have weaker connectivity between the premotor and the auditory regions have better motor skills. The precuneus, an important locus of the default mode network, was found to have increased local resting connectivity in children with ADHD. Local connectivity has been shown to decrease with age in TD children<sup>9</sup>. The relative increase in local connectivity within both DMN and “task-positive” networks involving the pre-SMA thereby suggests that ADHD is associated with a delay in this typical maturational process. In summary, children with ADHD exhibit increased local resting connectivity in a task-positive network involving the pre-SMA, and in the default mode network, when compared to TD children.

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**Funding** NIH NCRP P41 RR15241; NIH RO1 R01 NS047781; NIH RO1 MH085328; NIH RO1 MH078160