fMRI Evidence of Increasing Disengagement of Sustained Attention-Related Activation with Increasing Age in ADHD Children

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BACKGROUND: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a lack of age-appropriate impulse control, excessive activity levels, and inattention. Structural and biochemical neuroimaging studies have identified differences in neurodevelopmental trajectories of frontostriatal and frontoparietal attention networks in ADHD compared with typically developing (TD) individuals. Specifically, we have shown a lack of progressive maturation in the prefrontal cortex of children with ADHD[1,2]. Task-based functional MRI (fMRI) studies of sustained attention have likewise characterized activation differences predominately in the right hemisphere of ADHD children; however, the impact of ADHD on neurodevelopment of attentional networks from a functional perspective has not been assessed. In this cross-sectional study, a task-based fMRI paradigm of sustained attention was used to assess age-related differences in the functional activation of ADHD children and adolescents compared to TD individuals. We hypothesize an increasing functional disengagement with age in the dorsal prefrontal cortex (dPFC) of ADHD reflecting a dysmaturation of the attention network.

SUBJECTS AND METHODS: A total of 14 children with DSM-IV ADHD (13M+1F; mean age 10.6±2.5 yrs; mean FS-IQ 105±14; 9 with the combined subtype and 5 with the predominantly inattentive type) and 18 TD (16M+2F; mean age 10.2±2.3 yrs; mean FS-IQ 100±11) participated in a fMRI study using a sustained attention task-based the Conners Continuous Performance Test[3] (CPT-II). All ADHD children were free of psycho-stimulant medication for at least a 24-hour period prior to the MR examination.

The fMRI protocol included collecting gradient echo echo planar images (TR: 2.6s, TE: 29ms, FOV: 256mm^2, acquisition matrix: 128x128, 36 axial slices, pixel dimension: 2x2x3mm^3,) on a 3T Siemens Verio system using a 12-channel volume head coil. During the task, subjects were instructed to attend to sequences of rapidly presented numbers (1 or 2 digits) blocked in 120s epochs presented and indicate by button press when a target ("0" or "00") appeared in the sequence. Pure rest epochs (30s) were used between task epochs to provide a pure resting baseline against which to contrast attention-related activity (118 MRI volumes total).

Functional MRI images were preprocessed with SPM8 using a standard protocol, including realignment to the first volume in the series, correction for susceptibility-by-movement interactions, normalization, and smoothing with an 6mm full width at half maximum isotropic Gaussian kernel (1.5mm^3). In first-level analyses, windows of interest treated as boxcar wave forms were convolved with the canonical hemodynamic response function (HRF) to produce reference wave forms for contrast assessment (Attention > Rest) within the General Linear Model framework. Motion effects were modeled using the six movement parameters (translation and rotation) as covariates of no interest. Age-related differences between ADHD and TD in the response of regions of interest were assessed in a second level analysis of covariance with group as a single factor, age as a covariate (interacting with group), and gender and FSIQ as additional covariates. Directional contrasts (TD*Age > ADHD*Age; ADHD*Age > TD*Age) were used to identify clusters where age-related increases in the attention-related response in one group exceeded the other. All fMRI analyses were spatially thresholded in 4 regions of interest that included the dorsal prefrontal cortex (dPFC; BA 9 & 46), the anterior cingulate cortex (ACC), the basal ganglia (BG) and the parietal lobe (PL)[4] and cluster level significance in the regions of interest (p<.05)[5].

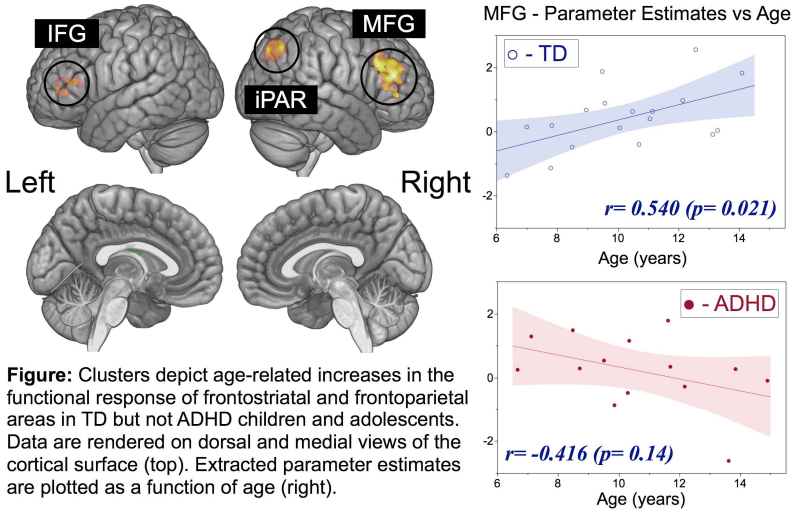

Figure: Clusters depict age-related increases in the functional response of frontostriatal and frontoparietal areas in TD but not ADHD children and adolescents. Data are rendered on dorsal and medial views of the cortical surface (top). Extracted parameter estimates are plotted as a function of age (right).

RESULTS: Across the four regions of interest, significant interactions with TD*Age > ADHD*Age were present in the right middle frontal gyrus (BA 46/9; kE=722; p= 0.001), right inferior parietal lobe (BA 40; kE=839; p= 0.001) and in the left inferior frontal gyrus (BA 45/46; kE= 162; p= 0.003) (see Figure). The extracted parameter estimates showed increasing contrast with age between diagnostic groups in the sustained attention-related activations [e.g., a positive correlation with age in TD (r= 0.540 and p= 0.021) contrasted with a negative correlation with age in ADHD (r= -0.416 and p=0.14)] (see Figure). Regarding the opposite contrast of ADHD*Age > TD*Age, there was a significant cluster in the left caudate (kE=78; p= 0.007).

CONCLUSIONS: These results show significant age-related functional responses of core attention-related frontostriatal and frontoparietal areas are altered in children and adolescents with ADHD relative to TD individuals. Though based on cross-sectional data, the developmental dynamics of ADHD relative to their TD counterparts are different. In particular, ADHD children appear to show age-related decreases in the fMRI response of frontal and parietal areas, suggestive of a relative disengagement of these areas with increasing age. These results are not only novel in providing a developmental context to previous demonstrations of hypoactivation in response to attention in ADHD[6], but also in providing consistency and an extension to our previous findings supporting a dPFC dysmaturation in ADHD children[1,2].

[1]Stanley JA, et al. *Psychiatry Res.* 2006; 148: 217-221. [2]Stanley JA, et al. *Arch. Gen. Psychiatry* 2008; 65 (12): 1419-1428. [3]Conners C, et al. *J Abnorm Child Psychol.* 2003; 31(5): 555-562. [4]Maldjian JA, et al. Neuroimage. 2003; 19(3): 1233-1239. [5]Ward BD. Simultaneous inference for fMRI data. Milwaukee, WI: Medical College of Wisconsin; 2000. [6]Rubia, K., et al. Hum Brain Mapp, 2006; 27, 973-993.