Developmental Deviation in the Cortico-Striatal Response in Children with ADHD: fMRI Evidence using a Sustained Attention Task

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Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in children, which is not well understood in terms of its course of illness in children. Using i*n vivo* ^{31}P spectroscopy, we have shown age-related deficits in the prefrontal cortex of ADHD children with greatest contrast in the older children[1,2]. The data suggests a lack of a progressive neurodevelopment in ADHD children, yet the functional basis of this effect has not been investigated using fMRI. In this cross-sectional study, we investigated whether ADHD children would show a similar lack of age-related changes in sustained attention performance compared to healthy control (HC) children. We hypothesized that HC children will show an age-related increase in the fMRI BOLD response to attention performance, which will be absent in ADHD children.

Subjects and Methods: A total of 16 children with DSM-IV ADHD (14M+2F; mean age 9.9±2.1 yrs; mean FS-IQ 104±14; 12 with the combined subtype and 4 with the predominantly inattentive type) and 12 HC (9M+3F; mean age 9.3±2.2 yrs; mean FS-IQ 98±10) 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 HC 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 (HC*Age > ADHD*Age; ADHD*Age > HC*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].

Results: Across the four regions of interest, age-related increases in the fMRI BOLD response were significant in HC but not in the ADHD children. Significant clusters (p<.05) are rendered on dorsal and medial surface projections with maxima (voxel level) observed in the superior parietal cortex (sPL; x=60, y=-45, z=39; t_{22}=3.61, p<.001), BG (x=33, y=-10, z=0; t_{22}=3.23, p<.002), ACC (x=4, y=38, z=22; t_{22}=2.33, p<.02) and dPFC (x=-38, y=23, z=37; t_{22}=2.2, p<.02) (Figure 1). The opposite contrast of age-related increases in ADHD children did not reveal significant clusters.

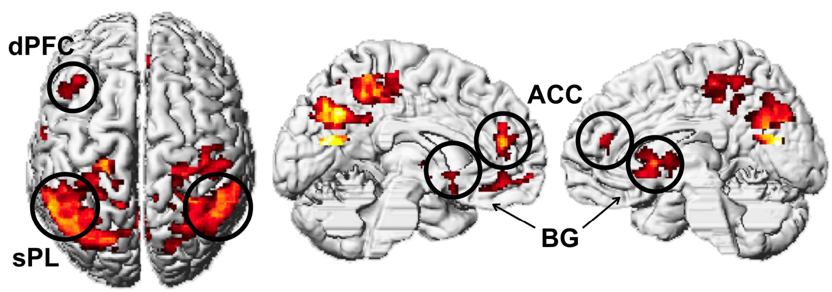

Figure 1. Clusters depict age-related increases in the functional response of cortico-striatal regions (insets; see text for labels) in HC but not ADHD children and adolescents. Data are rendered on dorsal and medial views of the cortical surface.

Conclusions: These results suggest that the developmental trajectory of the functional response of core attention-related cortico-striatal regions is altered in children and adolescents with ADHD relative to HC. The observed age-related increase in functional engagement in HC children and adolescents provides an important extension to previously documented patterns (in older samples)[6], and suggests that functional plasticity of the healthy brain response begins early in childhood and continues through early adolescence. The results also provide novel evidence of the early deviation in the functional response in ADHD progressively diverging from controls through the critical period of adolescence.

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