Brain Activation Gradients in Ventrolateral Prefrontal Cortex Related to Persistence of ADHD in Adolescent Boys

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ABSTRACT

Objective: To explore the possible role that functional abnormalities of the prefrontal cortex and basal ganglia play in the persistence of attention-deficit/hyperactivity disorder (ADHD) in adolescents aged 15 to 19 years.

Method: Ten male adolescents who were diagnosed with ADHD during childhood were grouped in to those who continued to meet full diagnostic criteria for DSM-IV ADHD (persisters; n = 5) and those in whom symptoms had remitted sufficiently to warrant a diagnosis of ADHD in partial remission (remitters; n = 5). Persisters, remitters, and five carefully matched controls with no history of ADHD were scanned using functional magnetic resonance imaging while performing a go/no-go task.

Results: Parallel linear trends were found in performance on the go/no-go task and activation of ventrolateral prefrontal cortex, such that persisters made the most commission errors (33%) and showed the greatest activation, remitters made fewer commission errors (24%) and had lower activity, and activation was lowest in controls who made the fewest errors (13%). Conclusions: These preliminary results suggest that developmental changes in ADHD symptomatology are associated with functional changes in ventrolateral prefrontal cortex activity. J. Am. Acad. Child Adolesc. Psychiatry, 2005;44(1):47–54. Key Words: attention-deficit/hyperactivity disorder, adolescence, functional magnetic resonance imaging, prefrontal cortex, development.

Convergent lines of research have implicated impairments of frontostriatal brain regions and the inhibitory control functions that they purportedly mediate in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Neuropsychological studies have historically noted the similarity in inhibitory deficits between individuals with ADHD and patients with frontal lobe lesions (Mattes, 1980; Pontius, 1973). Structural magnetic resonance imaging (MRI) studies of children with ADHD have consistently reported reduced volumetric measures of the prefrontal cortex (Castellanos et al., 1996; Filipek et al., 1997) and caudate nucleus (Castellanos et al., 1996, 2002; Filipek et al., 1997) as well as of afferent regions in the parietal cortex (Filipek et al., 1997) and cerebellum (Castellanos et al., 1996, 2002). More recent studies using functional MRI (fMRI) have found attenuated striatal activation and enhanced prefrontal cortical activity in young children and latency-aged boys with ADHD performing go/no-go tasks (Durston et al., 2003; Vaidya et al., 1998). In contrast, activation of the prefrontal cortex and striatum were both reduced in adolescents with ADHD during the Stop task (Rubia et al., 1999). Finally, adults with ADHD activated prefrontal cortex and striatal regions during the Stroop task instead of the anterior cingulate activation seen in controls (Bush et al., 1999).
Notwithstanding the compelling evidence of frontostriatal abnormalities in ADHD, the precise nature of the pathophysiology has remained elusive. The developmental course of these neural abnormalities and their relation to ADHD symptomatology across the life span is also unclear. Symptoms of ADHD typically emerge during the preschool years (Campbell, 1995) and often persist into early adulthood (Barkley et al., 1990). Yet, many children with ADHD experience a diminution of hyperactive and, to a lesser extent, inattentive symptoms during late childhood and adolescence (Biederman et al., 2000; Hill and Schoener, 1996). Little is known about the determinants of the ADHD symptom course, but recent neuroimaging findings point to developmental changes in the nature of the frontostriatal abnormalities in ADHD. Cross-sectional (Castellanos et al., 1996) and longitudinal (Castellanos et al., 2002) studies have both found that caudate nucleus volume reductions in ADHD are most prominent in late childhood and seem to normalize during adolescence, which coincides with the waning of hyperactive symptoms frequently seen in afflicted individuals (Biederman et al., 2000; Hill and Schoener, 1996). On the contrary, the reduced cerebellar volume identified in children with ADHD seems to continue throughout adolescence (Castellanos et al., 2002), raising the possibility that cerebellar anomalies are involved in the persistence of ADHD. As such, investigation of adolescents diagnosed with ADHD during childhood, but who vary with regard to current diagnosis, may yield answers regarding the developmental course of neural abnormalities in ADHD.

The purpose of these exploratory analyses was to examine the possible relationship between frontostriatal brain function during response inhibition and the persistence or remission of ADHD in adolescence. Ten adolescents who were diagnosed with ADHD during childhood were scanned with fMRI while performing a go/no-go task. Half of these adolescents continued to meet full diagnostic criteria for DSM-IV ADHD (persisters) and half had experienced sufficient symptomatic remission to warrant a diagnosis of ADHD in partial remission (remitters). A carefully matched control group of five adolescent males with no history of ADHD was also scanned during performance of the go/no-go task. Based on the limited available data, we tested for brain activation gradients related to the diverse outcomes of ADHD in adolescence. Specifically, we predicted that ventral prefrontal cortex activation will be greatest in persisters and lowest in controls, with remitters falling between the two groups. Conversely, it is expected that striatal activation will be lowest in persisters, somewhat greater in remitters, and greatest in controls.

**METHOD**

**Participants**

Ten adolescent males (nine right handed, one left handed) who were diagnosed with DSM-III-R ADHD when they were aged 7 to 11 years were recruited from a larger pool of participants in a study of ADHD conducted between 1990 and 1994 (Halperin et al., 1994, 1997). A diagnosis of schizophrenia, pervasive developmental disorder, major affective disorder, Tourette’s syndrome, or a Full Scale IQ below 70 were exclusionary criteria in the initial study. The adolescents were reevaluated for the current study on average 8.8 years (SD = 1.1) after their childhood assessment. Adolescents and their parents were interviewed separately using the NIMH Diagnostic Interview Schedule for Children–Version IV (NIMH-DISC) (Shaffer et al., 2000), and the two reports were combined using an either-parent-or-adolescent algorithm (i.e., adding symptoms reported by either source) to diagnose ADHD and other psychiatric disorders (Jensen et al., 1995; Schwab-Stone et al., 1996). Parents also rated the severity of various disruptive behaviors using the Child Behavior Checklist (CBCL) (Achenbach, 1991). General cognitive ability was assessed with the WISC-III (Wechsler, 1991) or WAIS-III (Wechsler, 1987) depending on age.

The adolescents with childhood ADHD were classified as persisters or remitters based on whether they met full diagnostic criteria for DSM-IV ADHD in adolescence, as determined by the combined patient and parent reports on the NIMH-DISC. Five of the 10 patients in the study met diagnostic criteria for DSM-IV ADHD in partial remission as defined by fewer than six symptoms in both the inattentive and hyperactive-impulsive domains and were classified as remitters, while five patients continued to meet full diagnostic criteria for DSM-IV ADHD and were classified as persisters. Among the latter group, one patient met full criteria for the combined type of ADHD, three met criteria for the predominantly inattentive type, and one for the predominantly hyperactive-impulsive type. However, the latter four patients should not truly be considered to have the predominantly inattentive and hyperactive-impulsive types of ADHD. Rather, they were children with combined type ADHD who had high numbers of both inattentive and hyperactive-impulsive symptoms and experienced a diminution of symptoms with age (Biederman et al., 2000; Hill and Schoener, 1996). One of the persisters also met criteria for conduct disorder, but there were no reports of any other Axis I disorders. As shown in Table 1, persisters and remitters did not differ significantly during childhood in age, Full Scale IQ, ADHD symptom count, or the Attention Problems factor of the CBCL. One persister and one remitter had a comorbid diagnosis of conduct disorder in childhood and the latter also met diagnostic criteria for separation anxiety disorder. Four patients in the persister group and three in the remitter group had a history of treatment with stimulant medications, but no patient received medication for ADHD in the 6 months before this study.
Skin.
sequence with the following parameters: TR = 2000 milliseconds; TE = 40 milliseconds; flip angle = 90 degrees; slice thickness = 5 mm; 2.5 mm skip; field of view = 23 cm; 64 × 64 matrix. Participants completed three runs of 200 seconds each resulting in 100 time points per adolescent.

Statistical Analyses

Group differences in the behavioral data were analyzed using a one-way analysis of variance (ANOVA), in which the percentage of commission errors on NOGO trials served as the dependent variable. Image preprocessing and analyses were conducted using statistical parametric mapping (SPM99) (www.fil.ion.bma.ac.uk/spm), as described in detail elsewhere (Schulz et al., 2004). Briefly, the functional scans were realigned to the first volume, coregistered to the high-resolution 3D-SPGR image, normalized to a standard template (Montreal Neurological Institute), and spatially smoothed. General linear modeling was then conducted for the functional scans from each subject by modeling the observed event-related blood oxygenation level–dependent signals and regressors to identify the relationship between the experimental parameters and the hemodynamic response. Event-related analyses were performed using the default SPM basis function, which consists of a synthetic hemodynamic response function composed of two gamma functions and its derivative (Friston et al., 1998). Regressors were created by convolving a train of delta functions (representing the sequence of individual trials) with the SPM basis function. The linear combination of all the regressors was used to model the hemodynamic response to four conditions: correct and incorrect NOGO and GO trials. The six parameters generated during motion correction were entered as covariates. The images for each participant were collapsed into a single image for each of the four conditions.

The specific effects of response inhibition were tested by applying appropriate linear contrasts to the parameter estimates for the correct NOGO minus correct GO contrast, resulting in a contrast map for each participant. The contrast images of all participants were entered into a second-level group analysis conducted with a random-effects statistical model that accounted for intrasubject variability and permitted population-based inferences to be drawn. The a priori hypotheses were tested with multiple regression models, in which group (i.e., persisters, remitters, controls) served as the dependent variable and activation during response inhibition was the independent variable. These analyses examined linear trends in activation patterns during NOGO trials versus GO trials across persisters, remitters, and controls. The resultant voxel-wise statistical maps were then thresholded for significance using a cluster-size algorithm that protects against an inflation of the false-positive rate. Results of a priori regions of interest are reported at an uncorrected height (intensity) threshold of p < .01 and an extent threshold of k = 120 voxels, corresponding to a whole-brain false-positive rate of approximately 0.01. Coordinates of activation were converted to the Talairach and Tournoux (1988) coordinate system using a nonlinear transformation (Brett, 2000) (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

RESULTS

Behavioral Data

There was a linear trend in behavioral performance on the go/no-go task, such that persisters made a greater percentage of commission errors on NOGO trials than remitters, who in turn made more errors than controls (mean ± SD: persisters, 32.7 ± 14.5; remitters, 24.4 ± 13.6; controls, 12.7 ± 11.9). However, this effect did not reach significance (F2.16 = 2.82, p = .09). Analysis of the six parameters generated during motion correction revealed no significant group differences in mean translational movement (mean ± SD: persisters, 0.44 ± 0.21 mm; remitters, 0.40 ± 0.43 mm; controls, 0.46 ± 0.18 mm; F2.12 = 0.06, p = not significant [NS]). Mean rotational displacement was less than 0.0 degrees for the three groups (F2.12 = 0.52, p = NS).

fMRI Data

Significant linear trends in brain activation during response inhibition (correct NOGO trials minus correct GO trials) across persisters, remitters, and controls were found in several brain regions. Markedly greater activation of Brodmann’s area (BA) 47 of the right (Talairach: x = 36, y = 24, and z = −16; cluster size = 355; tmax = 5.93; df = 1,12; p < .001) and left (Talairach: x = −34, y = 24, and z = −16; cluster size = 172; tmax = 3.82; df = 1,12; p = .001) ventrolateral convexity of the inferior frontal gyrus was seen in persisters than remitters, who in turn had greater activation than control subjects (Fig. 1). As shown in Figure 2, the per-
sisters had greater activation of this region for NOGO than GO trials, while remitters had nearly identical activity for both trial types, and controls conversely showed greater activation for GO than NOGO trials. A similar linear trend in activation across persisters, remitters, and controls was evident in the left inferior parietal lobule (BA 40) (Talairach: \(x = -48, y = -32,\) and \(z = 24;\) cluster size = 159; \(t_{\text{max}} = 3.61;\) \(df = 1,12;\) \(p = .001).\)

Significant linear trends in activation were also seen in the opposite direction, such that activation of right lingual gyrus (BA 19) (Talairach: \(x = 14, y = -52,\) and \(z = 12;\) cluster size = 572; \(t_{\text{max}} = 5.90;\) \(df = 1,12;\) \(p < .001)\) and right medial occipital gyrus (BA 19) (Talairach: \(x = 32, y = -72,\) and \(z = 7;\) cluster size = 159; \(t_{\text{max}} = 6.31;\) \(df = 1,12;\) \(p = .001)\) was greater in controls relative to remitters, who showed more activity than persisters. No such trends were found for striatal activation.

**DISCUSSION**

To our knowledge, this study provides the first evidence that the commonly described developmental changes in ADHD symptomatology may be related to functional changes in prefrontal cortex. Among adolescents who were diagnosed with ADHD during childhood, activation of ventrolateral prefrontal cortex (VLPFC) during response inhibition differed between those in whom ADHD symptoms persisted and those in whom symptoms had remitted and between both of these groups and a carefully matched group of controls with no history of ADHD. Specifically, activation of the VLPFC paralleled performance on the go/no-go task, such that activity was greatest in persisters who made the most commission errors, was lower in remitters who made fewer errors, and was lowest in controls who made the fewest errors. In fact, activation of this prefrontal region in control subjects was increased when responding and decreased during inhibition, with greater activation seen in individuals who had more difficulty inhibiting the prepotent response. A similar linear trend in activation was found in the left inferior parietal lobule. In contrast, bilateral occipital activation was greater in controls relative to remitters, who showed more activity than persisters. Surprisingly, predicted differences in striatal activation across persisters, remitters, and controls were not found.

Several lines of evidence have implicated the VLPFC in the inhibitory control of cognition and behavior. The VLPFC receives nonspatial visual input from inferotemporal cortex (Ungerleider et al., 1989), input regarding the valence of expected outcomes from basolateral amygdala (Kita and Kitai, 1990), and mnemonic input from parahippocampal regions (Deacon et al., 1990) and, in turn, uses this convergence of information to modulate behavior through projections to premotor regions (Lu et al., 1994). The VLPFC is unique among prefrontal regions in that it contains a population of neurons that code for sensory cues that signal the suppression of responses based on the salience or association of these cues with reward (Sakagami et al., 2001; Schoenbaum et al., 1998), with some of these neurons responding selectively to visual cues signaling inhibition in go/no-go tasks (Sakagami et al., 2001). This cue-selective activity precedes response execution (Sakagami et al., 2001) and is influenced by interference from past stimulus-response associations (Lauwereyns et al., 2001). In contrast, neuroimaging studies of humans have generally localized response inhibition in a more superior region of the VLPFC (Bunge et al., 2002; Durston et al., 2003;
Menon et al., 2001). Thus, the poor inhibitory control and enhanced activation of VLPFC seen in persisters and to a lesser extent in remitters in this study may reflect difficulties with suppressing interference from task-inappropriate responses rather than with the actual inhibition of responses.

The unexpected finding of activation gradients in more posterior brain regions raises the possibility that brain abnormalities in ADHD extend beyond the VLPFC to afferent regions. Remitters and to a lesser extent persisters activated a posterior parietal region that is part of the dorsal visual pathway that mediates spatial-selective processing (Mishkin et al., 1983), suggesting greater interference from task-inappropriate visuospatial cues. In contrast, controls and remitters activated bilateral occipital regions of the ventral visual pathway that mediate feature-selective processing (Mishkin et al., 1983). The lack of this activity in persisters suggests difficulties with attentional tuning to stimulus features (Thiel et al., 2004).

The current finding of increased VLPFC activation in adolescents with childhood ADHD is partially consistent with two previous fMRI studies that used go/no-go tasks in young children and latency-aged boys with ADHD (Durston et al., 2003; Vaidya et al., 1998). Both of those studies reported increased ventral prefrontal cortical activity and attenuated striatal activation in children with ADHD. These data suggest that the enhanced neural activation seen in adolescents with childhood ADHD in this study may reflect a continuation of inhibitory control deficits from childhood. At the same time, the apparent reduction in VLPFC activation in adolescents who no longer present with ADHD suggests that neural activity normalized to some extent with the remission of symptomatology. The lack of findings in the striatum in this study was unexpected but is not totally inconsistent with the reported developmental trajectory of caudate nucleus anomalies in ADHD (Castellanos et al., 1996, 2002). Reduced caudate nucleus volumes in ADHD are reported to be most prominent in late childhood and to normalize during adolescence. Thus, it is possible that the participants in the current study were beyond the age of maximal differences in striatal activation.

The enhanced VLPFC activation in adolescents with childhood ADHD in the current study and the possibility that this abnormal activation may diminish with the developmental decline of symptomatology are not consistent with a previous report of reduced ventral prefrontal cortex activation in adolescents with ADHD performing the Stop task (Rubia et al., 1999). This inconsistency is not all that surprising given the task-dependent nature of the neural contributors to response inhibition (Mostofsky et al., 2003). Alternately, the discrepancy between the studies may reflect the uniqueness of the current sample. The patients in this study were not self-referred during adolescence but were instead diagnosed with ADHD as children and followed into adolescence and as such presented with varying degrees of symptomatology. Self-referral of adolescents with ADHD is associated with numerous selection biases as well as concerns regarding the veracity of retrospective recall of childhood symptoms (Mannuzza et al., 2002) and has consistently generated different findings from those reported in longitudinal studies (Marks et al., 2001).

The current study provides preliminary evidence that the commonly described developmental changes in ADHD symptomatology may be related to functional changes in VLPFC activity. There were parallel linear trends in the ability to inhibit prepotent responses and activation of VLPFC such that adolescents who continued to present with ADHD made the most errors and showed the greatest activation, adolescents in whom symptoms of ADHD had remitted made fewer errors and had lower activity, and activation was lowest in adolescents with no history of ADHD who made the fewest errors. These data raise the possibility that poor inhibitory control in adolescents with childhood ADHD may be related to impairments in using incentive or motivational information to guide behavioral responding and that these deficits and the correspondingly enhanced VLPFC activation may normalize with the remission of symptomatology over development.

Limitations

These findings must be considered in the context of several important methodological limitations, particularly the exploratory nature of the analyses and the small and all male sample. It is very possible that greater statistical power in the current study would have revealed significant group differences in activation of other regions in the brain (e.g., striatum). Further, the go/no-go task used in this study also had several limitations. First, the comparison of GO trials that...
required motor responses and NOGO trials that did not involve responses introduced motor activity as a potential confounding factor in the analyses. However, this is less of an issue in group comparisons like the current study than in single-group designs because the three groups serve as controls for each other. Second, the preponderance of GO trials to NOGO trials required to create the prepotent tendency to respond in the task also yielded more data points for GO than NOGO trials, which may have skewed the analyses toward the effects of the former. Thus, we cannot completely rule out that our findings reflect the effects of motor control processes rather than inhibitory control processes.

Clinical Implications

The current findings contribute to the growing body of scientific evidence regarding the pathophysiology of ADHD and place these findings in a developmental context. Further, these results provide some insight into the developmental changes of ADHD symptoms and neuropsychological correlates across adolescence that are frequently seen in clinical practice. However, the current findings do not directly affect diagnosis and treatment practices for ADHD at this time. The identification of brain activation abnormalities using fMRI techniques currently requires analysis of group-averaged data that do not lend itself to individual case study. Future innovations and advances in the field may ultimately establish fMRI as a useful technique to help establish diagnoses, follow individuals over time, or monitor the effects of medication on brain function (e.g., Vaidya et al., 1998).

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