Published in final edited form as:

Cortex. 2017 May ; 90: 1–11. doi:10.1016/j.cortex.2017.01.019.

Prefrontal and Parietal Correlates of Cognitive Control Related to the Adult Outcome of Attention-Deficit/Hyperactivity Disorder Diagnosed in Childhood

Kurt P. Schulz^{a,*}, Xiaobo Li^{a,b,1}, Suzanne M. Clerkin^c, Jin Fan^{a,d}, Olga G. Berwid^e, Jeffrey H. Newcorn^a, and Jeffrey M. Halperin^{a,d}

^aDepartment of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^bDepartment of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, USA

^cDepartment of Psychology, Purchase College of the State University of New York, Purchase, NY, USA

^dDepartment of Psychology, Queens College of the City University of New York, Flushing, NY, USA

^eDepartment of Behavioral Sciences, York College of the City University of New York, Jamaica, NY, USA

Abstract

The protracted and highly variable development of prefrontal cortex regions that support cognitive control has been purported to shape the adult outcome of attention-deficit/hyperactivity disorder (ADHD). This neurodevelopmental model was tested in a prospectively followed sample of 27 adult probands who were diagnosed with ADHD in childhood and 28 carefully matched comparison subjects aged 21 – 28 years. Probands were classified with persistent ADHD or remitted ADHD. Behavioral and neural responses to the stimulus and response conflict task performed during functional magnetic resonance imaging were compared in probands and comparison subjects and in probands with persistent and remitted ADHD. Response speed and accuracy for stimulus, response, and combined conflicts did not differ across groups. Orbitofrontal, inferior frontal and parietal activation was lower in probands than comparison subjects, but only for combined conflicts, when demand for cognitive control was highest. Reduced activation for combined conflicts in probands was almost wholly attributable to the persistence of ADHD; orbitofrontal, inferior frontal, anterior cingulate and parietal activation was

*Corresponding author. Department of Psychiatry, Box 1230, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. kurt.schulz@mssm.edu (K.P. Schulz).

¹Shared first authors.

Declaration of Interest

Dr. Newcorn is a recipient of research grants from Enzymotec, Lundbeck and Shire, and has received consultancy fees from Alcobra, Cerecor, Enzymotec, Ironshore, Neos, NFL, NLS, Pearson, Rhodes, Shire, Sunovion, Supernus, and Teva. The other authors report no potentially competing interests.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

lower in probands with persistent ADHD than both probands with remitted ADHD and comparison subjects, but did not differ between probands with remitted ADHD and comparison subjects. These data provide the first evidence that prefrontal and parietal activation during cognitive control parallels the adult outcome of ADHD diagnosed in childhood, with persistence of symptoms linked to reduced activation and symptom recovery associated with activation indistinguishable from adults with no history of ADHD.

Keywords

Prefrontal cortex; cognitive control; development; attention-deficit/hyperactivity disorder; adults

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and impairing neurodevelopmental disorder that has a highly variable course over the lifespan (Barkley, 2016). Symptoms of inattention and hyperactivity-impulsivity typically emerge during the preschool years (Campbell, 1995) and frequently diminish during late childhood and adolescence (Lahey et al., 2016; Sasser, Kalvin, & Bierman, 2016). Yet, up to 65% of children with ADHD continue to present with symptoms into adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002; Faraone, Biederman, & Mick, 2006), with significant functional (Barkley, 2016; Gjervan, Torgersen, Nordahl, & Rasmussen, 2012) and cognitive (Bedard, Trampush, Newcorn, & Halperin, 2010; Halperin, Trampush, Miller, Marks, & Newcorn, 2008) impairment. Little is known about the neural mechanisms that determine the developmental course of ADHD and the persistence or remission of symptoms in adulthood (Steinhausen, 2009), although it has been proposed that optimal development of prefrontal cortex regions that support cognitive control throughout childhood and adolescence is linked to better outcomes (Halperin & Schulz, 2006). Delineation of neural correlates of the variable outcomes of ADHD has heuristic value for understanding the pathophysiology of the disorder. It further offers the potential to improve clinical prediction and prevention, and to aid in the development of interventions targeted at mechanisms associated with recovery.

Lateral prefrontal and posterior parietal cortices that support cognitive control have been implicated in both the etiology (Brennan & Arnsten, 2008; Casey, Nigg, & Durston, 2007) and developmental remission of ADHD (Halperin & Schulz, 2006). Findings of similar deficits in prefrontal and parietal activation related to cognitive control in children, adolescents, and adults with ADHD have been purported to reflect a core pathophysiology that remains relatively static over the lifespan (Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; McCarthy, Skokauskas, & Frodl, 2014). However, abnormalities in medial and lateral prefrontal anatomy, activation, and connectivity associated with ADHD have been found to be age-dependent (Bollmann et al., 2015) and to vary as a function of adult outcome (Clerkin et al., 2013; Franck et al., 2015; Mattfeld et al., 2014; Shaw et al., 2006, 2013, 2015; Wetterling et al., 2015). In general, persistence of ADHD into adulthood has been associated with increased prefrontal cortical thinning (Shaw et al., 2006, 2013), lower white matter integrity in prefrontal tracts (Shaw et al., 2015), and reduced prefrontal activation (Wetterling et al., 2015) and functional connectivity with

caudal and subcortical regions (Clerkin et al., 2013; Franck et al., 2015; Mattfeld et al., 2014; Wetterling et al., 2015), while symptomatic remission has been linked to the normalization of prefrontal structure (Shaw et al., 2006, 2013) and function (Clerkin et al., 2013; Franck et al., 2015; Mattfeld et al., 2014; Wetterling et al., 2015). The relatively late and protracted maturation of prefrontal cortex may influence the pathophysiology of ADHD and contribute to the remission of symptoms (Halperin & Schulz, 2006). Nevertheless, there is little evidence yet which links this prefrontal maturation specifically to cognitive control processes. This can only be tested in prospectively followed children with ADHD who vary in adult outcome.

This study used functional magnetic resonance imaging (fMRI) with the Stimulus and Response Conflict Task (SRCT; Nassauer & Halperin, 2003) to test prefrontal and parietal activation for cognitive control in a prospectively followed sample of young adults diagnosed with ADHD in childhood and well-matched comparison subjects with no history of ADHD. The prospective design allowed for the comparison of activation in adults with childhood ADHD who had substantial remission of symptoms and those with persistent ADHD. The SRCT provides separate measures of 1) conflict between competing stimulus features, 2) conflict between prepotent and correct responses, and 3) the combination of stimulus and response conflicts. Our neurodevelopmental model of ADHD (Halperin & Schulz, 2006) and findings using the SRCT in adolescents diagnosed with ADHD during childhood (Bedard et al., 2010; Schulz et al., 2005) suggested that persistence of ADHD into adulthood would be associated with prefrontal cortical deficits related to cognitive control. Specifically, we predicted that young adults with persistent ADHD would show reduced prefrontal activation for the SRCT conflict conditions compared to adults with childhood ADHD that has remitted and adults with no history of ADHD. It was further predicted that the developmental improvements in prefrontal cognitive control mechanisms purportedly associated with the remission of ADHD symptoms would result in comparable prefrontal activation for SRCT conflict conditions in adults with childhood ADHD that has remitted and adults with no history of ADHD.

2. Method

2.1. Participants

Participants were 27 adult probands who were diagnosed with combined-type ADHD when they were 7 – 11 years old and 28 adult comparison subjects with no history of ADHD. The probands were recruited from a study of ADHD conducted between 1990 and 1997 (Halperin et al., 1994, 1997, 2003). Childhood diagnoses of ADHD were determined using multiple parent and teacher ratings of ADHD symptoms and confirmed with the Diagnostic Interview Schedule for Children version 2 (Shaffer et al., 1996; Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989). Exclusion criteria for the original childhood study included chronic medical illness; neurological disorder; diagnosis of schizophrenia, autism spectrum disorder, or chronic tic disorder; Full Scale IQ < 70; and not speaking English. The comparison group was recruited from the same communities where the probands resided several years later for an adolescent follow-up study (Miller, Miller, Newcorn, & Halperin, 2008). Comparison subjects had no history of childhood ADHD and no more than three

inattentive or hyperactive-impulsive symptoms reported by parents on the Diagnostic Interview Schedule for Children – Version 4 (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). Psychiatric disorders that were allowed in the childhood ADHD sample were not exclusionary for the comparison group.

The adult assessments were conducted a mean $\pm$ SD of 15.08 ± 1.29 years after the probands' childhood evaluation. The study was approved by the institutional review boards of Queens College of CUNY and the Icahn School of Medicine at Mount Sinai. Participants provided signed informed consent and were compensated for their time and travel expenses. Probands and comparison subjects were interviewed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002), supplemented by a semi-structured interview for ADHD that was adapted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997) and the Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein, Johnson, & Conners, 2006). The adapted interview was previously shown to demonstrate strong internal consistency in this sample ($\alpha = 0.92$) (Clerkin et al., 2013). The psychiatric status of the probands reflected the diverse adult outcomes characteristic of ADHD (Faraone et al., 2006). Eleven (41%) probands met DSM-5 diagnostic criteria for ADHD in adulthood and were classified with persistent ADHD, including four (15%) with combined presentation, four (15%) with predominantly inattentive presentation, one (4%) with predominantly hyperactive-impulsive presentation, and two (7%) with unspecified ADHD. Sixteen (59%) probands endorsed no more than three inattentive or three hyperactive-impulsive symptoms and no more than a total of five symptoms in adulthood, and were classified with remitted ADHD. None of the comparison subjects met diagnostic criteria for ADHD in adulthood or reported more than three inattentive or hyperactive-impulsive symptoms in the past six months.

Clinical and demographic characteristics of the sample are presented in Table 1. Probands and comparison subjects, and probands with persistent and remitted ADHD, did not differ in age, handedness, race, ethnicity, or the prevalence of anxiety, mood, and substance use disorders. As expected, ADHD symptom count on the semi-structured interview and ratings on the Conners Adult ADHD Rating Scale (CAARS; Conners, Erhardt, & Sparrow, 1999) were greater for probands than comparison subjects, as well as for probands with persistent ADHD compared to those with remitted ADHD. Ten (91%) probands with persistent ADHD and ten (63%) with remitted ADHD had a history of treatment with psychostimulant medication ($\chi^2 = 2.74$, $p = 0.10$). Mean $\pm$ SD length of treatment was 5.70 ± 3.66 years for probands with persistent ADHD and 4.40 ± 3.89 years for those with remitted ADHD ($t_{18} = 0.77$, $p = 0.45$). None of the participants were currently being treated with psychostimulants, and potential participants who were being treated with other psychotropic medications at the time of the study were excluded. Positive urine toxicology results for amphetamines, opiates, and cocaine were exclusionary. Participants refrained from cannabis use for at least 24 hours before the fMRI scan.

2.2. Image Acquisition

All participants were scanned on the same 3.0-T Siemens Allegra (Siemens, Erlangen, Germany) head dedicated MRI scanner. A high resolution T2-weighted anatomical volume of the brain was acquired in the axial plane with a turbo spin-echo pulse sequence (TR = 4,050 ms, TE = 99 ms, flip angle = 170°, field of view = 240 mm, matrix = 512 × 336, 40 slices, slice thickness = 4 mm, in-plane resolution = 0.41 mm²). Functional T2*-weighted images depicting the blood-oxygen-level-dependent (BOLD) signal were acquired at the same 40 slice locations as the T2 image using gradient-echo echo-planar images (TR = 2,500 ms, TE = 27 ms, flip angle = 82°, matrix = 64 × 64, slice thickness = 4 mm, in-plane resolution = 3.75 mm²). Stimuli were projected onto a rear projection screen mounted at the head of the magnet bore that was viewed through a mirror on the head coil.

2.3. Experimental Task

A blocked-design Stimulus and Response Conflict Task (SRCT) was implemented in this study (Nassauer & Halperin, 2003; Schulz et al., 2005). The SRCT generates separate measures of: (a) stimulus conflict; (b) response conflict; and (c) combined conflicts. The three measures share the same stimuli, responses, and control conditions that do not involve conflict, and differ only in the context of the stimulus-response associations. As shown in Figure 1, the SRCT consisted of six 32-s blocks that were each preceded by 30 s of fixation and 5 s during which task instructions (e.g., “Press where the arrow is pointing”) were displayed. The six blocks each consisted of 16 trials in which the stimulus appears along the vertical midline for 500 ms, with a 1500-ms ISI denoted by a central fixation-cross. Trials were randomized with regard to right and left location and direction of stimuli. Participants were instructed to respond with optical buttons held in each hand. Each run of the SRCT lasted 7 min 22 s and included 10-s fixation periods at the beginning and end of each run. Participants each completed three runs.

The first three blocks of the SRCT assessed conflict between stimulus features associated with competing response options. Participants responded to the direction of centrally displayed arrows in block 1, the location of rectangles on the left or right side of the screen in block 2, and the direction of arrows on the left or right side of the screen in block 3. Randomization of trials in block 3 resulted in conflict between arrow direction and location (e.g., right-pointing arrow on left side) on 50% of trials. The neural effects of stimulus conflict in block 3 were isolated by subtracting out the neural effects of processing direction cues in block 1 and location cues in block 2.

The fourth and fifth blocks tested conflict between prepotent and competing responses associated with the same stimulus feature. Block 4 was identical to block 1 and was repeated to re-establish arrow direction as the prepotent response. Block 5 required participants to respond in the opposite direction of centrally displayed arrows and involved conflict between the prepotent and correct responses on all trials. The neural effects of response conflict in block 5 were isolated by subtracting out the neural effects of processing direction cues in block 4.

The sixth block tested conflicts between both competing stimulus features and prepotent and correct responses. Participants responded in the opposite direction of left- or right-pointing arrows presented on the left and right side of the screen. Randomization of trials resulted in conflict between arrow direction and location on 50% of trials, while all trials involved conflict between the prepotent and correct responses. The neural effects of combined stimulus and response conflicts in block 6 were isolated by subtracting out the neural effects of processing both direction cues in blocks 1 and 4 and location cues in block 2

2.4. Imaging Data Preprocessing

The task-based functional images and high resolution T2-weighted structural images were preprocessed using the FEAT fMRI analysis tool in FSL 5.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The functional images were individually corrected for slice timing, head motion, and spatial intensity for each participant, and then spatially smoothed with an 8mm full-width and half maximum Gaussian kernel. A high-pass temporal filter of 0.01 Hz was used to remove low-frequency noise. Non-brain structures in the functional and structural images were extracted using the Brain Extraction Tool (Smith, 2002). Next, the functional images were aligned to the skull-stripped structural image individually for each participant using an affine translation, and were then registered to the MNI152 template using a linear registration (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). Finally, three frame-wise variables were calculated from the six realignment parameters generated during motion correction: i) the absolute values of the differentials of the time courses; ii) the sum of the absolute values of the differentials of the realignment parameters (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012); and iii) the mean motion (mean of the absolute values of the displacements along x-, y-, and z-axes compared to the previous volume). The functional images were regressed for each participant individually on the three frame-wise variables, along with the six realignment parameters and three nuisance variables (white matter, CSF, global signal), to remove motion-related signal artifacts. Functional time series with mean motion > 0.2 mm were excluded from further analysis.

Voxel-based functional activation maps were generated for the stimulus conflict, response conflict, and combined conflict conditions for each participant using the FEAT GLM analysis tool in FSL 5.0. The resultant Z (Gaussianized T/F) statistic images were thresholded using clusters established at $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$

2.5. Statistical Analyses

Mean reaction times (RT) and the percentages of both incorrect responses and omission errors were calculated for each of the six blocks in the SRCT. Separate mixed-design analyses of variance (ANOVA) with stimulus conflict (presence vs. absence) and response conflict (presence vs. absence) as within-subject factors and group as the between-subject factor were used to compare mean RT, incorrect responses, and omission errors between 1) probands and comparison subjects and 2) probands with remitted and persistent ADHD. The two-tailed p value for significance was set at 0.05 for all analyses.

The stimulus conflict, response conflict, and combined conflict activation maps for all participants were entered into separate random-effect general linear models (GLM) that included sex as a fixed-effect covariate. The Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a cluster corrected significance threshold of $p < 0.05$.

3. Results

3.1. Behavioral Results

Mean RT and the percentages of incorrect responses and omission errors for the four conflict conditions on the SRCT are summarized in Table 2. The ANOVA assessing mean RT in probands and comparison subjects revealed significant main effects of stimulus conflict ($F_{1,53} = 78.43$, $p < 0.001$, $\eta^2 = 0.60$) and response conflict ($F_{1,53} = 38.77$, $p < 0.001$, $\eta^2 = 0.42$), as well as a significant interaction between the two conflicts in the combined condition ($F_{1,53} = 6.98$, $p = 0.01$, $\eta^2 = 0.12$). The analysis of mean RT in probands with remitted and persistent ADHD also found significant main effects of stimulus conflict ($F_{1,25} = 56.29$, $p < 0.001$, $\eta^2 = 0.69$) and response conflict ($F_{1,25} = 19.51$, $p < 0.001$, $\eta^2 = 0.44$), and a small but non-significant interaction between the two conflicts ($p = 0.14$, $\eta^2 = 0.08$). Neither ANOVA found a main effect of group (both $p > 0.65$, $\eta^2 < 0.01$) or group $\times$ conflict interaction (all $p > 0.20$, $\eta^2 < 0.05$).

Similar results were found for the percentage of correct responses, with significant main effects of stimulus conflict for the proband versus comparison subject analysis ($F_{1,53} = 5.75$, $p = 0.02$, $\eta^2 = 0.10$) and the remitted versus persistent ADHD analysis ($F_{1,25} = 6.68$, $p = 0.02$, $\eta^2 = 0.21$), and small but non-significant main effects of response conflict for both comparisons (both $p > 0.05$, $\eta^2 < 0.07$). There were no significant main effects of group, interactions between stimulus and response conflicts, or group $\times$ conflict interactions (all $p > 0.20$, $\eta^2 < 0.07$). A third ANOVA testing omission errors yielded no significant main effects and no significant conflict $\times$ group interaction (all $p > 0.20$, $\eta^2 < 0.07$).

3.2. Neuroimaging Results

3.2.1. Stimulus conflict—Probands and comparison subjects demonstrated similar patterns of frontoparietal activation for conflict between competing stimulus features, including overlapping regions of frontal operculum, inferior frontal gyrus, middle frontal gyrus, dorsolateral prefrontal cortex (DLPFC), superior parietal lobule, and precuneus (see eFig. 1 and eTable 1 of the Supplement). Direct comparison of the groups found no differences in activation for stimulus conflict between either probands and comparison subjects or probands with remitted and persistent ADHD.

3.2.2. Response Conflict—The conflict between competing responses was associated with activation in left inferior and superior parietal cortex in comparison subjects (see eFig. 2 and eTable 2 of the Supplement). Probands showed no significant activation for response conflict and group comparisons revealed no significant differences in activation between either probands and comparison subjects or probands with remitted and persistent ADHD.

3.2.3. Combined Conflicts—Activation for dual stimulus and response conflicts was found in superior parietal lobule and precuneus in both probands and comparison subjects, but only comparison subjects showed activation in frontal operculum and supplementary motor area (see eFig. 3 and eTable 3 of the Supplement). As shown in the top panel of Fig. 2A, direct comparison of the groups revealed significantly lower activation in probands than comparison subjects in widely dispersed regions that included right orbitofrontal cortex, inferior frontal gyrus pars orbitalis, and adjacent middle temporal gyrus, as well as bilateral cerebellum, left middle temporal gyrus, and right lingual gyrus, and precuneus, inferior parietal lobule, and middle and superior occipital gyri. Regions of between-group differences are listed in Table 3.

Further between-group comparisons revealed a pattern of significantly diminished frontoparietal activation for combined stimulus and response conflicts in probands with persistent ADHD compared to probands with remitted ADHD that is detailed in Table 4. The bottom panel of Fig. 2A shows that probands with persistent ADHD had reduced activation in left anterior cingulate cortex, right orbitofrontal cortex, and ventral, orbital, and triangular aspects of right and left inferior frontal gyrus, as well as bilateral inferior and superior parietal lobules, and left posterior cingulate cortex. Conflict-related activation was also lower in bilateral temporal regions and left cerebellum in probands with persistent ADHD compared to those with remitted ADHD. Post-hoc comparisons found that frontoparietal activation was significantly lower in probands with persistent ADHD than comparison subjects, but did not differ between the remitted ADHD and comparison groups. Fig. 2B illustrates that the mean magnitude of activation in left inferior frontal gyrus, anterior cingulate cortex, and superior parietal lobule in probands with remitted ADHD was closer to the mean magnitude in comparison subjects than the magnitude in probands with persistent ADHD.

4. Discussion

Longitudinal follow-up of adult probands diagnosed with ADHD in childhood revealed deficits in prefrontal and posterior parietal activation for cognitive control that varied as a function of adult outcome. Probands with childhood ADHD showed reduced activation for stimulus and response conflicts in regions ranging from inferior frontal gyrus and orbitofrontal cortex to inferior parietal lobule, precuneus, visual cortex, and cerebellum relative to comparison subjects with no history of ADHD. However, lower frontoparietal activation among probands relative to comparison subjects was almost completely attributable to the persistence of ADHD in adulthood. Conflict-related activation in inferior frontal gyrus, orbitofrontal cortex, anterior cingulate cortex, inferior and superior parietal lobules, and cerebellum was lower in probands with persistent ADHD compared to both probands with remitted ADHD and comparison subjects. Yet, frontoparietal activation was deficient only when demand for cognitive control was greatest, in response to dual stimulus and response conflicts, and was not associated with deficits in the accuracy or speed of responses. Most significantly, probands with remitted ADHD and comparison subjects did not differ in neural or behavioral responses to stimulus and response conflicts. Thus, frontoparietal activation for cognitive control may parallel symptom recovery in adults with

childhood ADHD and seems to be more sensitive to current clinical status than to cognitive control performance.

The current finding of reduced orbitofrontal and inferior frontal activation for conflict in probands with persistent ADHD converges with findings from a previous report that linked the persistence of ADHD in adulthood to lower fractional anisotropy in the uncinate and inferior fronto-occipital fasciculi (Shaw et al., 2015), which connect these prefrontal regions to limbic and visual areas, respectively (Hau et al., 2016). Reduced fractional anisotropy in the inferior fronto-occipital tract and decreased inferior frontal activation for cognitive control are consistent findings in adults with a current diagnosis of ADHD (Cubillo et al., 2010, 2011; Konrad et al., 2012; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009). However, examined prospectively, adults with childhood ADHD who no longer met diagnostic criteria did not differ from controls in orbitofrontal and inferior frontal activation in the current study or related fractional anisotropy in the prior study (Shaw et al., 2015). This convergence of structural and functional findings suggest that white matter microstructural anomalies may underlie deficits in prefrontal activation associated with the persistence of ADHD in adulthood, and the remission of symptoms may reflect the developmental normalization of white matter microstructure that results in improved prefrontal activation for cognitive control. Evidence that orbitofrontal activation for reversal learning varied as a function of adult ADHD outcome suggests that the developmental changes involved in symptom remission may involve reward and reinforcement mechanisms (Wetterling et al., 2015).

Orbitofrontal cortex and inferior frontal gyrus and the related uncinate and inferior fronto-occipital fasciculi are among the last regions and tracts in the brain to mature functionally, with development beginning in late childhood and continuing into early adulthood (Gogtay et al., 2004; Lebel & Beaulieu, 2011). The time course of this inferior prefrontal maturation fits well with the developmental decline in symptoms seen in many individuals with ADHD (Faraone et al., 2006). The degree to which prefrontal maturation ameliorates pre-existing deficits in cognitive control has been proposed as a key determinant of the developmental trajectory of ADHD (Halperin & Schulz, 2006).

Our results are also partially consistent with findings from a prospective study of adolescents with ADHD that reported an association between symptom improvement and increased resting state connectivity in anterior cingulate cortex (Francx et al., 2015). However, that study also found greater connectivity in rostral prefrontal cortex in adolescents with remitted ADHD compared to healthy controls but not adolescents with persistent ADHD. In contrast, in the current study, anterior cingulate and ventral prefrontal activation for conflict were reduced in adults with persistent ADHD relative to those with remitted ADHD and comparison subjects, but did not differ between the remitted ADHD and comparison groups. This pattern of results suggests that the remission of ADHD involves the developmental normalization of prefrontal deficits rather than the development of compensatory prefrontal functions proposed in the previous study (Francx et al., 2015). The discrepant findings regarding the role of prefrontal function in the remission of ADHD may reflect differences between the adolescent and adult samples or task-based and resting state neuroimaging

methods, although it must be noted that resting state connectivity in medial prefrontal cortex did not differ between adults with persistent and remitted ADHD (Mattfeld et al., 2014).

The finding that superior parietal lobule activation for conflict varied as a function of adult ADHD outcome was unexpected but not surprising given that this region supports cognitive control (Buschman & Miller, 2007) and is commonly co-activated with inferior frontal gyrus and anterior cingulate cortex during cognitive control (Niendam et al., 2012). Reduced superior parietal activation is a hallmark deficit of ADHD (Cortese et al., 2012; Hart et al., 2013) and has been linked to impaired attention allocation (Tamm, Menon, & Reiss, 2006), sustained attention (Christakou et al., 2013), and interference control (Vloet et al., 2010). Functional maturation of posterior parietal regions begins in middle childhood and is mostly complete by adolescence (Gogtay et al., 2004). This time course coincides with both the observed gradual improvement in attentional capacity and control (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001) and the onset of the developmental decline in ADHD symptoms (Faraone et al., 2006). Nevertheless, little is known about the contribution of superior parietal maturation to the remission of ADHD.

The present study failed to replicate previous findings of behavioral deficits in cognitive control linked to the persistence of ADHD in a larger sample of adolescents from which the current subjects were subsequently recruited in adulthood (Bedard et al., 2010; Halperin et al., 2008). These studies found that among adolescents diagnosed with ADHD in childhood, the persistence of symptoms was associated with poor working memory and impaired sustained attention (Halperin et al., 2008), as well as slow responses to stimulus conflict on the SRCT (Bedard et al., 2010). The discrepant findings in relation to behavioral deficits may be due to differences in the SRCT used in the current and previous studies. The shortened and modified task used in the current study may not have challenged the adults sufficiently to detect group differences in performance. Alternatively, developmental differences between the adult sample in the current study and the adolescent samples in the previous studies may account for the observed differences in cognitive control deficits. Neuropsychological measures of cognitive control have not been found to consistently distinguish the persistence and remission of ADHD in adulthood (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013).

The results of this study must be considered in the context of several possible methodological limitations. First, the sample was defined by the presence or absence of ADHD in childhood, and as is commonly the case in longitudinal studies, many of the participants presented with other psychiatric disorders, histories of stimulant treatment, and substance (cannabis) use at adult outcome. We did not exclude participants for these conditions to avoid recruiting a non-representative ADHD sample or a 'supernormal' comparison group. The rates of cannabis use and other psychiatric disorders did not differ significantly across the comparison and ADHD groups, and the 20 probands with a history of stimulant treatment were evenly split across the persistent ADHD and remitted ADHD subgroups. Further, the behavioral and neuroimaging results remained unchanged after controlling for other diagnoses, cannabis use, or treatment history. Therefore, we have confidence that that our results can be attributed to the persistence versus remission of ADHD rather than more generalized psychopathology, substance use, or treatment. Second,

the small but non-significant difference in the gender ratio of probands with persistent ADHD and those with remitted ADHD may have contributed to our findings of neural differences. Third, the blocked design of the SRCT used in the study precluded the separate modeling of conflict-related and error-related activation; thus, error-related activation may have contributed to the findings of group differences in prefrontal and parietal activation. Finally, the generalizability of the results are limited by the use of a conflict task to study cognitive control. It is likely that we would have found group differences in activation in at least some other brain regions had we used another cognitive control task (e.g., working memory).

In conclusion, our results provide the first evidence that inferior prefrontal and superior parietal activation during cognitive control differs as a function of the persistence or remission of ADHD in adulthood – with persistence linked to reduced activation (as seen in children with ADHD) and remission of symptoms associated with activation similar to comparison subjects without a history of ADHD. Larger prospective studies with fMRI data collected at multiple time points are needed to more fully understand the developmental trajectory of prefrontal and parietal correlates of cognitive control and the role of these mechanisms in the persistence and/or remission of ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by National Institutes of Health grants R01MH060698 (to Jeffrey M. Halperin), K01MH070892 (to Kurt P. Schulz), and KL2RR029885 (to Suzanne M. Clerkin). The sponsors had no role in the planning or conduct of the study or in the interpretation of the results.

References

- Anderson VA, Anderson P, Northam E, Jacobs R, Catroppa C. Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology*. 2001; 20(1):385–406. DOI: 10.1207/S15326942DN2001_5 [PubMed: 11827095]
- Barkley RA. Recent longitudinal studies of childhood attention-deficit/hyperactivity disorder: Important themes and questions for further research. *Journal of Abnormal Psychology*. 2016; 125(2):248–255. DOI: 10.1037/abn0000125 [PubMed: 26854509]
- Barkley RA, Fischer M, Smallish L, Fletcher K. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. *Journal of Abnormal Psychology*. 2002; 111(2):279–289. [PubMed: 12003449]
- Bedard AC, Trampush JW, Newcorn JH, Halperin JM. Perceptual and motor inhibition in adolescents/young adults with childhood-diagnosed ADHD. *Neuropsychology*. 2010; 24(4):424–434. DOI: 10.1037/a0018752 [PubMed: 20604617]
- Bollmann, S., Ghisleni, C., Poil, SS., Martin, E., Ball, J., Eich-Hochli, D., ... Brandeis, D. *World Journal of Biological Psychiatry*. 2015. Age-dependent and -independent changes in attention-deficit/hyperactivity disorder (ADHD) during spatial working memory performance; p. 1-12.
- Brennan AR, Arnsten AF. Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. *Annals of the New York Academy of Sciences*. 2008; 1129:236–245. DOI: 10.1196/annals.1417.007 [PubMed: 18591484]

- Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science*. 2007; 315(5820):1860–1862. DOI: 10.1126/science.1138071 [PubMed: 17395832]
- Campbell SB. Behavior problems in preschool children: a review of recent research. *Journal of Child Psychology and Psychiatry*. 1995; 36(1):113–149. [PubMed: 7714027]
- Casey BJ, Nigg JT, Durston S. New potential leads in the biology and treatment of attention deficit-hyperactivity disorder. *Current Opinions in Neurology*. 2007; 20(2):119–124. DOI: 10.1097/WCO.0b013e3280a02f78
- Christakou A, Murphy CM, Chantiluke K, Cubillo AI, Smith AB, Giampietro V, ... Rubia K. Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with autism. *Molecular Psychiatry*. 2013; 18(2):236–244. DOI: 10.1038/mp.2011.185 [PubMed: 22290121]
- Clerkin SM, Schulz KP, Berwid OG, Fan J, Newcorn JH, Tang CY, Halperin JM. Thalamo-cortical activation and connectivity during response preparation in adults with persistent and remitted ADHD. *American Journal of Psychiatry*. 2013; 170(9):1011–1019. DOI: 10.1176/appi.ajp.2013.12070880 [PubMed: 24030612]
- Conners, CK., Erhardt, D., Sparrow, MA. *Conners' Adult ADHD Rating Scales (CAARS)*. New York: Multi-Health Systems; 1999.
- Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*. 2012; 169(10):1038–1055. DOI: 10.1176/appi.ajp.2012.11101521 [PubMed: 22983386]
- Cubillo A, Halari R, Ecker C, Giampietro V, Taylor E, Rubia K. Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. *Journal of Psychiatric Research*. 2010; 44(10):629–639. DOI: 10.1016/j.jpsychires.2009.11.016 [PubMed: 20060129]
- Cubillo A, Halari R, Giampietro V, Taylor E, Rubia K. Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. *Psychiatry Research*. 2011; 193(1):17–27. DOI: 10.1016/j.psychres.2010.12.014 [PubMed: 21601434]
- Epstein, JN., Johnson, D., Conners, CK. *Conners' Adult ADHD Diagnostic Interview for DSM-IV*. North Tonawanda, NY: Multi-Health Systems; 2006.
- Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine*. 2006; 36(2):159–165. DOI: 10.1017/S003329170500471X [PubMed: 16420712]
- First, MB., Spitzer, RL., Gibbon, M., Williams, JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I-NP)*. New York: Biometrics Institute, New York State Psychiatric Institute; 2002.
- Franx W, Oldehinkel M, Oosterlaan J, Heslenfeld D, Hartman CA, Hoekstra PJ, ... Mennes M. The executive control network and symptomatic improvement in attention-deficit/hyperactivity disorder. *Cortex*. 2015; 73:62–72. DOI: 10.1016/j.cortex.2015.08.012 [PubMed: 26363140]
- Gjervan B, Torgersen T, Nordahl HM, Rasmussen K. Functional impairment and occupational outcome in adults with ADHD. *Journal of Attention Disorders*. 2012; 16(7):544–552. DOI: 10.1177/1087054711413074 [PubMed: 21725028]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, ... Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101(21):8174–8179. DOI: 10.1073/pnas.0402680101 [PubMed: 15148381]
- Halperin JM, Newcorn JH, Schwartz ST, Sharma V, Siever LJ, Koda VH, Gabriel S. Age-related changes in the association between serotonergic function and aggression in boys with ADHD. *Biological Psychiatry*. 1997; 41(6):682–689. DOI: 10.1016/S0006-3223(96)00168-0 [PubMed: 9066992]

- Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*. 2006; 132(4):560–581. DOI: 10.1037/0033-2909.132.4.560 [PubMed: 16822167]
- Halperin JM, Schulz KP, McKay KE, Sharma V, Newcorn JH. Familial correlates of central serotonin function in children with disruptive behavior disorders. *Psychiatry Research*. 2003; 119(3):205–216. [PubMed: 12914892]
- Halperin JM, Sharma V, Siever LJ, Schwartz ST, Matier K, Wornell G, Newcorn JH. Serotonergic function in aggressive and nonaggressive boys with attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 1994; 151(2):243–248. DOI: 10.1176/ajp.151.2.243 [PubMed: 8296897]
- Halperin JM, Trampush JW, Miller CJ, Marks DJ, Newcorn JH. Neuropsychological outcome in adolescents/young adults with childhood ADHD: profiles of persisters, remitters and controls. *Journal of Child Psychology and Psychiatry*. 2008; 49(9):958–966. DOI: 10.1111/j.1469-7610.2008.01926.x [PubMed: 18573145]
- Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 2013; 70(2):185–198. DOI: 10.1001/jamapsychiatry.2013.277 [PubMed: 23247506]
- Hau J, Sarubbo S, Perchey G, Crivello F, Zago L, Mellet E, ... Petit L. Cortical Terminations of the Inferior Frontal-Occipital and Uncinate Fasciculi: Anatomical Stem-Based Virtual Dissection. *Frontiers in Neuroanatomy*. 2016; 10:58.doi: 10.3389/fnana.2016.00058 [PubMed: 27252628]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17(2):825–841. [PubMed: 12377157]
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*. 2001; 5(2):143–156. [PubMed: 11516708]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(7):980–988. DOI: 10.1097/00004583-199707000-00021 [PubMed: 9204677]
- Konrad A, Dielentheis TF, El Masri D, Dellani PR, Stoeter P, Vucurevic G, Winterer G. White matter abnormalities and their impact on attentional performance in adult attention-deficit/hyperactivity disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 2012; 262(4):351–360. DOI: 10.1007/s00406-011-0251-1 [PubMed: 21879383]
- Lahey BB, Lee SS, Sibley MH, Applegate B, Molina BS, Pelham WE. Predictors of adolescent outcomes among 4–6-year-old children with attention-deficit/hyperactivity disorder. *Journal of Abnormal Psychology*. 2016; 125(2):168–181. DOI: 10.1037/abn0000086 [PubMed: 26854503]
- Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*. 2011; 31(30):10937–10947. DOI: 10.1523/JNEUROSCI.5302-10.2011 [PubMed: 21795544]
- Mattfeld AT, Gabrieli JD, Biederman J, Spencer T, Brown A, Kotte A, Kagan E, Whitfield-Gabrieli S. Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain*. 2014; 137(Pt 9):2423–2428. DOI: 10.1093/brain/awu137 [PubMed: 24916335]
- McCarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. *Psychological Medicine*. 2014; 44(4):869–880. DOI: 10.1017/S0033291713001037 [PubMed: 23663382]
- Miller CJ, Miller SR, Newcorn JH, Halperin JM. Personality characteristics associated with persistent ADHD in late adolescence. *Journal of Abnormal Child Psychology*. 2008; 36(2):165–173. DOI: 10.1007/s10802-007-9167-7 [PubMed: 17701339]
- Nassauer KW, Halperin JM. Dissociation of perceptual and motor inhibition processes through the use of novel computerized conflict tasks. *Journal of International Neuropsychological Society*. 2003; 9(1):25–30.

- Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive Affective and Behavioral Neuroscience*. 2012; 12(2):241–268. DOI: 10.3758/s13415-011-0083-5
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012; 59(3):2142–2154. DOI: 10.1016/j.neuroimage.2011.10.018 [PubMed: 22019881]
- Sasser TR, Kalvin CB, Bierman KL. Developmental trajectories of clinically significant attention-deficit/hyperactivity disorder (ADHD) symptoms from grade 3 through 12 in a high-risk sample: Predictors and outcomes. *Journal of Abnormal Psychology*. 2016; 125(2):207–219. DOI: 10.1037/abn0000112 [PubMed: 26854506]
- Schulz KP, Tang CY, Fan J, Marks DJ, Newcorn JH, Cheung AM, Halperin JM. Differential prefrontal cortex activation during inhibitory control in adolescents with and without childhood attention-deficit/hyperactivity disorder. *Neuropsychology*. 2005; 19(3):390–02. DOI: 10.1037/0894-4105.19.3.390 [PubMed: 15910125]
- Shaffer D, Fisher P, Dulcan MK, Davies M, Piacentini J, Schwab-Stone ME, ... Regier DA. The NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA Study. Methods for the Epidemiology of Child and Adolescent Mental Disorders Study. *Journal of American Academy of Child and Adolescent Psychiatry*. 1996; 35(7):865–877.
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of American Academy of Child and Adolescent Psychiatry*. 2000; 39(1):28–38. DOI: 10.1097/00004583-200001000-00014
- Shaffer, D., Fisher, P., Piacentini, J., Schwab-Stone, M., Wicks, J. Diagnostic Interview Schedule for Children—Parent Version (DISC-2.1P). New York: New York Psychiatric Institute; 1989.
- Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 2006; 63(5):540–549. DOI: 10.1001/archpsyc.63.5.540 [PubMed: 16651511]
- Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2013; 74(8):599–606. DOI: 10.1016/j.biopsych.2013.04.007 [PubMed: 23726514]
- Shaw P, Sudre G, Wharton A, Weingart D, Sharp W, Sarlls J. White matter microstructure and the variable adult outcome of childhood attention deficit hyperactivity disorder. *Neuropsychopharmacology*. 2015; 40(3):746–754. DOI: 10.1038/npp.2014.241 [PubMed: 25241803]
- Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R. White-matter abnormalities in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Human Brain Mapping*. 2009; 30(9):2757–2765. DOI: 10.1002/hbm.20703 [PubMed: 19107752]
- Smith SM. Fast robust automated brain extraction. *Human Brain Mapping*. 2002; 17(3):143–155. DOI: 10.1002/hbm.10062 [PubMed: 12391568]
- Steinhausen HC. The heterogeneity of causes and courses of attention-deficit/hyperactivity disorder. *Acta Psychiatrica Scandinavica*. 2009; 120(5):392–399. DOI: 10.1111/j.1600-0447.2009.01446.x
- Tamm L, Menon V, Reiss AL. Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. *American Journal of Psychiatry*. 2006; 163(6):1033–1043. DOI: 10.1176/ajp.2006.163.6.1033 [PubMed: 16741204]
- van Lieshout M, Luman M, Buitelaar J, Rommelse NN, Oosterlaan J. Does neurocognitive functioning predict future or persistence of ADHD? A systematic review. *Clinical Psychology Review*. 2013; 33(4):539–560. DOI: 10.1016/j.cpr.2013.02.003 [PubMed: 23528892]
- Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49(4):356–367. [PubMed: 20410728]

Wetterling F, McCarthy H, Tozzi L, Skokauskas N, O'Doherty JP, Mulligan A, ... Frodl T. Impaired reward processing in the human prefrontal cortex distinguishes between persistent and remittent attention deficit hyperactivity disorder. *Human Brain Mapping*. 2015; 36(11):4648–4663. DOI: 10.1002/hbm.22944 [PubMed: 26287509]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.

Schematic representation of the Stimulus and Response Conflict Tasks (SRCT) illustrating one run of the blocked fMRI design and a single trial for each of the six blocks in the run. The six blocks were preceded by a 30-second fixation period (+) and began with instructions (i) displayed for 5 seconds. Each block consisted of 16 trials that required participants to press the button in either the left or right hand according to the task contingencies. The C indicates the side for the correct response in the example.

Fig. 2.

(a) Significantly lower activation for combined stimulus and response conflicts in young adults diagnosed with ADHD during childhood than comparison subjects with no history of ADHD and adults with persistent ADHD than adults with remitted ADHD. The figures were thresholded at $p < 0.05$ (cluster-corrected); the color bar indicates Z values. (b) Mean Z scores for activation in inferior frontal gyrus, anterior cingulate cortex, and superior parietal lobule clusters (denoted by green arrows) are plotted for comparison subjects and adults with persistent and remitted ADHD. Error bars indicate ± 1 S.D.

Table 1

Sample characteristics

Characteristic	Comparison subjects (N = 28)	Childhood ADHD (N = 27)	p value ^a	Remitted ADHD (N = 16)	Persistent ADHD (N = 11)	p value ^a
Age, mean (S.D.)	24.6 (2.0)	24.2 (1.9)	0.47	24.2 (1.5)	24.1 (2.5)	0.90
Gender, male, n (%)	24 (86)	24 (89)	0.47	15 (94)	9 (82)	0.07
Right-handed, n (%)	25 (89)	23 (85)	0.61	13 (81)	10 (91)	0.50
Race			0.29			0.56
African-American, n (%)	11 (39)	7 (26)		4 (25)	3 (27)	
Asian, n (%)	2 (7)	0 (0)		0 (0)	0 (0)	
Caucasian, n (%)	12 (43)	17 (63)		11 (69)	6 (55)	
More than one race, n (%)	3 (11)	3 (11)		1 (6)	2 (18)	
Hispanic ethnicity, n (%)	10 (36)	14 (52)	0.14	8 (50)	6 (55)	0.74
ADHD symptoms, mean (S.D.)	1.5 (2.4)	5.8 (4.3)	<0.001	3.0 (1.9)	9.9 (3.6)	<0.001
Conners' Adult ADHD Rating Scale						
Inattentive, mean (S.D.)	45.8 (8.9)	54.7 (12.9)	0.005	50.5 (10.4)	60.6 (14.9)	0.06
Hyperactive, mean (S.D.)	44.3 (6.5)	53.5 (12.4)	0.001	48.2 (10.0)	60.7 (12.2)	0.01
ADHD Total, mean (S.D.)	44.8 (8.4)	55.7 (14.5)	0.001	49.9 (11.9)	63.8 (14.4)	0.02
Mood disorder, n (%)	2 (7)	4 (15)	0.31	2 (13)	2 (18)	0.66
Anxiety disorder, n (%)	10 (36)	8 (30)	0.78	3 (19)	5 (45)	0.12
Substance disorder, n (%)	7 (25)	11 (40)	0.15	7 (44)	4 (36)	0.74

^a Group differences were analyzed with independent samples *t*-tests for continuous variables and Pearson's chi-squared tests for categorical variables.

Table 2

Behavioral performance on the stimulus and response conflicts task (SRCT)

Variable	Comparison subjects (<i>N</i> = 28) Mean (S.D.)	Childhood ADHD (<i>N</i> = 27) Mean (S.D.)	Remitted ADHD (<i>N</i> = 16) Mean (S.D.)	Persistent ADHD (<i>N</i> = 11) Mean (S.D.)
Reaction time (ms)				
Control condition	471 (94)	472 (92)	465 (76)	486 (114)
Stimulus conflict	512 (94)	526 (109)	526 (109)	526 (114)
Response conflict	503 (101)	529 (130)	526 (119)	533 (150)
Combined conflict	588 (144)	598 (162)	592 (134)	607 (203)
Incorrect responses (%)				
Control condition	3.2 (5.6)	4.1 (5.3)	3.5 (3.9)	5.1 (7.1)
Stimulus conflict	5.4 (12.4)	7.7 (8.3)	6.2 (6.5)	10.2 (10.1)
Response conflict	5.2 (11.3)	7.9 (10.4)	5.1 (5.6)	11.7 (14.2)
Combined conflict	8.6 (17.3)	8.7 (13.9)	7.0 (5.9)	11.4 (21.6)
Omission errors (%)				
Control condition	0.3 (0.5)	0.4 (0.5)	0.3 (0.3)	0.4 (0.6)
Stimulus conflict	0.5 (1.1)	0.7 (0.7)	0.5 (0.6)	0.9 (0.9)
Response conflict	0.3 (0.6)	0.4 (0.9)	0.4 (0.5)	0.8 (1.5)
Combined conflict	0.8 (1.5)	0.8 (1.3)	0.6 (0.5)	0.8 (1.8)

Table 3

Clusters of lower activation for combined stimulus and response conflicts in (a) probands with childhood ADHD relative to comparison subjects and (b) probands with persistent ADHD compared to probands with remitted ADHD

Region	Cluster size ^d	p value	Z value	Coordinates ^b		
				x	y	z
(a)						
Left cerebellum	11,874	<0.0001	3.56	-18	-38	-20
Left middle temporal gyrus (BA 21)			3.53	-46	8	-22
Right cerebellum			3.37	8	-46	-38
Right lingual gyrus (BA 18)			3.29	20	-78	0
Right inferior frontal gyrus (BA 47)	6,272	<0.0001	3.23	42	16	-20
Right middle temporal gyrus (BA 21)			3.20	54	6	-20
Right orbitofrontal cortex (BA 11)			3.11	16	50	-12
Right superior occipital gyrus (BA 19)	2,098	0.048	3.69	32	-86	30
Right precuneus (BA 7)			2.89	10	-72	40
Right inferior parietal lobule (BA 39)			2.81	54	-62	20
Right middle occipital gyrus (BA 19)			2.71	44	-80	20
(b)						
Right superior parietal lobule (BA 7)	4,157	<0.0001	3.37	-30	-50	50
Left paracentral lobule (BA 5)			3.31	-2	-32	50
Left anterior cingulate cortex (BA 24)	2,849	0.0003	3.62	-14	30	22
Left inferior frontal gyrus (BA 47)			3.52	-32	38	0
Left inferior frontal gyrus (BA 45)			3.41	-52	28	20
Right orbitofrontal cortex (BA 11)	2,339	0.0013	4.01	24	34	-12
Right superior temporal gyrus (BA 22)			3.44	46	2	-14
Right middle frontal gyrus (BA 8)			3.08	32	12	44
Right inferior frontal gyrus (BA 10)			3.05	38	46	-16
Right inferior parietal lobule (BA 39)	2,023	0.0033	3.40	42	-68	22
Right inferior parietal lobule (BA 40)	1,707	0.0088	3.63	42	-40	42
Right superior parietal lobule (BA 7)			3.39	26	-46	50
Left fusiform gyrus (BA 37)	1,628	0.0113	3.45	30	-56	-2

Region	Cluster size ^a	p value	Z value	Coordinates ^b		
				x	y	z
Left cerebellum			3.06	-30	-34	-30

BA, Brodmann area.

^aNumber of voxels.

^bMontreal Neurological Institute coordinates (x, y, z) refer to the peaks of activation within each cluster.