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Brain Differences Between Persistent and Remitted Attention-Deficit/Hyperactivity Disorder

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Running title: Prospective Brain Differences in ADHD

Abstract

Prior resting-state studies examining the brain basis of attention-deficit/hyperactivity disorder have not distinguished between patients who persist versus those who remit from the diagnosis as adults. To characterize the neurobiological differences and similarities of persistence and remittance, we performed resting-state functional magnetic resonance imaging in individuals who had been longitudinally and uniformly characterized as having or not having attention-deficit/hyperactivity disorder in childhood and again in adulthood (16 years after baseline assessment). Intrinsic functional brain organization was measured in patients who had a persistent diagnosis in childhood and adulthood ($n = 13$), in patients who met diagnosis in childhood but not in adulthood ($n = 22$), and in control participants who never had attention-deficit/hyperactivity disorder ($n = 17$). A positive functional correlation between posterior cingulate and medial prefrontal cortices, major components of the default-mode network, was reduced only in patients whose diagnosis persisted into adulthood. A negative functional correlation between medial and dorsolateral prefrontal cortices was reduced in both persistent and remitted patients. The neurobiological dissociation between the persistence and remittance of attention-deficit/hyperactivity disorder may provide a framework for the relation between the clinical diagnosis, which indicates the need for treatment, and additional deficits that are common, such as executive dysfunctions.

Key Words: ADHD; default-mode network; fMRI; posterior cingulate cortex; longitudinal

Abbreviations: Attention-deficit/hyperactivity disorder = ADHD; blood oxygenation level-dependent = BOLD; default mode network = DMN; dorsolateral prefrontal cortex = DLPFC; Familywise Error = FWE; functional magnetic resonance imaging = fMRI; medial prefrontal cortex = MPFC; Montreal Neurological Institute = MNI; posterior cingulate cortex = PCC

Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by age-inappropriate inattention, impulsiveness, and hyperactivity, is one of the most common neurodevelopmental disorders, affecting 5-11% of school-aged children (Centers for Disease Control and Prevention, 2013). On average, ADHD is also associated with impairments in executive functions (Barkley, 1997), however there is considerable heterogeneity of such deficits (Willcutt *et al.*, 2005; Castellanos *et al.*, 2006). While, numerous functional neuroimaging studies in children and adults have revealed altered patterns of activation in ADHD during the performance of tasks of executive function (reviewed in Cortese *et al.*, 2012; Hart *et al.*, 2013), these studies examined ADHD patients who currently met diagnostic criteria for ADHD. The goal of the present study was to discover whether there are neurobiological differences between adults who persist with an ADHD diagnosis from childhood into adulthood (persistent ADHD) versus adults who had an ADHD diagnosis in childhood but no longer meet diagnostic criteria as adults (remitted ADHD). We investigated the possible distinction between persistence and remittance in ADHD by comparing brain functions among three longitudinally followed groups: (A) Patients with Persistent ADHD diagnoses in both childhood and adulthood; (B) Patients with Remitted ADHD who had met the diagnoses in childhood but no longer met that diagnosis in adulthood; and (C) Control participants documented as not having ADHD in either childhood or adulthood.

We used functional magnetic resonance imaging (fMRI) during the resting state to characterize intrinsic functional brain organization in the three groups of participants. Irregularities in brain networks at rest have emerged as a characteristic of brain

differences in ADHD (Castellanos *et al.*, 2008; Fair *et al.*, 2010; Uddin *et al.*, 2008).

Resting-state fMRI is a useful method for studying the pathophysiology of neurodevelopmental disorders because it can be obtained over a short period of time (~6 minutes) (Van Dijk *et al.*, 2010), is not confounded with task performance, and can be robust and reliable (Damoiseaux *et al.*, 2006; Shehzad *et al.*, 2009). Resting state fMRI assesses the correlation of blood oxygenation level-dependent (BOLD) signals across the brain. Brain regions exhibiting a positive temporal correlation are believed to be components of intrinsic functional networks.

One such network is the default mode network (DMN), which is comprised of brain regions typically more activated during rest than during task performance (Gusnard and Raichle, 2001). Regions in the DMN can also exhibit negative correlations (anticorrelations) with other brain regions that are activated for executive function (task-positive networks), such as the dorsolateral prefrontal cortex (DLPFC) (Fox *et al.*, 2005).

Resting-state studies of ADHD in both adults (Castellanos *et al.*, 2008; Uddin *et al.*, 2008) and children (Fair *et al.*, 2010) report reduced correlations between midline regions of the DMN and also reduced anticorrelations between DMN and task-positive networks. We examined two major nodes of the DMN, the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC), which have previously shown to be functionally hypoconnected in adults with ADHD (Castellanos *et al.*, 2008). We measured whole-brain positive correlations with the PCC region in order to compare functional connectivity within the DMN across groups (following Castellanos *et al.*, 2008). We also measured negative correlations with the MPFC region in order to compare functional connectivity between the DMN and a brain region associated with

executive function, the DLPFC (Miller and Cohen, 2001). The validity of these comparisons and observed results was strengthened by the fact that all participants were uniformly and prospectively assessed for ADHD and associated characteristics in both childhood and adulthood. Further, the childhood severity of ADHD (defined by the number of symptoms) did not differ between adults with persistent or remitted ADHD.

Materials and methods

Participants

Participants in the present study were derived from longitudinal follow-up studies of boys ($n = 29$) (Biederman *et al.*, 2012b) and girls ($n = 25$) (Biederman *et al.*, 2012a) with and without ADHD. Inclusion and exclusionary criteria can be found in the Supplemental materials. The current neuroimaging wave occurred approximately 16 years after baseline diagnosis, and all participants were characterized again near the time of the neuroimaging. Analyses were performed on 17 control participants, 13 ADHD participants who met persistent criteria, and 22 ADHD participants who met remitted criteria. Written informed consent was obtained from all participants following the guidelines outlined by the human research committees at Massachusetts General Hospital and the Massachusetts Institute of Technology.

Imaging Procedures and Analyses

Neuroimaging data were acquired on a 3 Tesla Siemens Trio scanner using a 32-channel head coil. Standard preprocessing and seed based functional connectivity analyses were performed combined with stringent motion artifact correction procedures (see Supplementary materials for detailed information).

Results

Demographic, Clinical, and Neuropsychological Results

All groups were well matched on both demographic and clinical variables (Supplementary Table 1). The Remitted and Persistent ADHD groups did not perform significantly different from one another on any neuropsychological measure, but both ADHD groups performed significantly worse than the Control group on multiple neuropsychological measures (Supplementary Table 3). See Supplementary materials for a detailed description of the behavioral results.

Neuroimaging Results

Posterior Cingulate Cortex Seed

The Control (*Fisher's* $z = 0.15$, $SD = 0.13$) and Remitted ADHD (*Fisher's* $z = 0.17$, $SD = 0.12$) groups exhibited positive correlations between the PCC and MPFC. In contrast, there was not a significant PCC-MPFC positive correlation in the Persistent ADHD group (Fig. 1A). Statistical tests between groups revealed significant reductions in PCC-MPFC positive correlations for the Persistent ADHD group relative to both the Control (Fig. 1B) and Remitted ADHD (Fig. 1C) groups. The Control and Remitted ADHD groups did not differ significantly from each other. These results held when participants were removed to match the groups on the amount of motion (Supplementary Fig. 3).

Figure 1

Medial Prefrontal Cortex Seed

The Control group exhibited significant negative correlations between the MPFC and bilateral DLPFC (*Fisher's z* = -0.12, *SD* = 0.16) (Fig. 2A). There were no significant negative correlations between the MPFC and DLPFC for either the Remitted or Persistent ADHD groups. When directly comparing whole-brain correlations of the MPFC seed in the Remitted and Persistent groups we did not observe significant differences in the DLPFC. Therefore, both groups were collapsed into a single group (All ADHD, *n* = 35) for subsequent MPFC-seed between-group comparisons. The ADHD group had significantly reduced negative correlations between the MPFC and left DLPFC compared to the Control group (Fig. 2B). At a slightly more liberal threshold (uncorrected *P* < 0.07, FWE cluster level correction *P* < 0.05), a similarly reduced negative correlation between the MPFC and right DLPFC was also observed in the ADHD group compared to the Control group. This suggests that the difference between groups was most likely bilateral in nature, with the difference being slightly below statistical threshold in the right DLPFC. Similar differences between MPFC and left DLPFC anticorrelations were observed when the ADHD and Control groups were statistically matched on the amount of motion (Supplementary Fig. 4). When subgroups equated for motion were examined, the Remitted ADHD group exhibited some above-threshold negative correlation in right DLPFC.

Figure 2

Discussion

We found neurobiological, circuit-specific differences and similarities in adults who were persistent in versus remitted from childhood diagnoses of ADHD. Differences in intrinsic functional brain organization within the DMN reflected the current adult diagnosis. The Persistent ADHD group exhibited reduced positive PCC-MPFC connectivity relative to both the Remitted ADHD and Control groups, whereas the Remitted ADHD and Control groups did not differ from one another. In contrast, reduced MPFC-DLPFC anticorrelation was related to childhood diagnosis of ADHD independent of adult diagnostic status. Both ADHD groups exhibited reduced negative MPFC-DLPFC connectivity relative to the Control group, and the Persistent and Remitted ADHD groups did not differ from one another.

The significant differences in intrinsic functional brain organization are salient because the three groups in adulthood were well characterized and well matched. They all received common diagnostic evaluations in childhood and adulthood. The findings are unlikely to reflect differences in the initial, childhood severity of ADHD, because childhood severity was similar in adults who had persistent or remitted ADHD. The two groups of adult ADHD patients exhibited many similar clinical characteristics that are associated with ADHD, including decreased IQ scores, impaired performance on a test of working memory, increased numbers of comorbidities, and increased complaints of daily executive functioning, but they did not differ significantly from one another on any of these characteristics. Despite the many similarities between the two ADHD groups, the Persistent and Remitted ADHD groups differed from one another by current diagnosis and by current functional brain organization.

Brain Differences Between Persistent and Remitted Groups

Dysfunction within the DMN as revealed by resting state functional connectivity appeared to reflect active ADHD symptoms (i.e., diagnostic state). In the present study, both the Control group and the Remitted ADHD group exhibited the typical positive correlations between the PCC and MPFC, two major midline nodes of the DMN. A prior study examining ADHD adults of a similar age range, by definition cases of persistent ADHD, discovered decreased PCC-MPFC correlations (Castellanos *et al.*, 2008). This noteworthy convergence of findings across these two studies, whether ADHD adults were recruited with retrospective determination of childhood ADHD or followed prospectively as in the present study, supports the syndromatic continuity between pediatric (Fair *et al.*, 2010) and adult ADHD (Castellanos *et al.*, 2008). The pattern of intrinsic DMN dysfunction was related to the current diagnostic state because the Persistent group differed reliably from both the Control group and Remitted ADHD group, who, in turn, did not differ from one another. The functional brain differences between Persistent and Remitted ADHD groups align with task-activation differences reported for persistent versus partially remitted ADHD groups (Schneider *et al.*, 2010; Schulz *et al.*, 2005).

Brain Similarities Between Persistent and Remitted Groups

Altered functional connectivity between MPFC and DLPFC appeared to reflect ever having been diagnosed with ADHD, irrespective of current diagnostic state. The Control group exhibited significant anticorrelations between MPFC and DLPFC, whereas neither the Remitted nor the Persistent groups exhibited an anticorrelation, and the Control group exhibited significantly greater left MPFC-DLPFC anticorrelation than the

combined ADHD groups. Greater negative correlation between the MPFC and DLPFC, an area associated with working memory and executive function (Hampson *et al.*, 2010), has been associated with greater working memory ability (Kelly *et al.*, 2008), and this negative correlation is reduced in other disorders that include executive dysfunction (Whitfield-Gabrieli *et al.*, 2009). Taken together, these findings suggest that reduced MPFC-DLPFC anticorrelation in ADHD is associated with cognitive weaknesses in executive functions that are frequently, but not definingly, impaired in ADHD. Indeed, in the present study the Remitted and Persistent ADHD groups both exhibited such cognitive impairments, and did not differ significantly from one another on any measure of working memory or executive function.

Attention-Deficit/Hyperactivity Disorder and Executive Functions

The present findings relate to emerging views on the relation between ADHD and executive functions. ADHD has been associated with impairments in executive functions (Barkley, 1997), but more recent evidence indicates a more variable relation between ADHD and executive functions (Castellanos *et al.*, 2006). For example, there is variability among ADHD patients as to which specific kinds of executive functions are impaired (e.g., inhibitory control vs. set shifting) (Willcutt *et al.*, 2005; Sonuga-Barke *et al.*, 2010). This variability was evident in the present study, with ADHD patients being impaired on some (spatial working memory, BRIEF), but not on other (inhibition and switching) measures of executive function.

More striking is evidence that as many as 50% to 70% of ADHD patients do not exhibit deficits in typical executive function tests such as response inhibition (Nigg *et al.*,

2005), but that patients who have both ADHD diagnoses and executive dysfunctions are at an especially high risk for occupational and academic underachievement (Biederman *et al.*, 2004). Furthermore, there is an apparent stability of neurocognitive dysfunction because ADHD patients who exhibit executive dysfunctions tend to persist in having such dysfunctions years later (Biederman *et al.*, 2007; Miller *et al.*, 2012).

The findings from the present study further support the partial dissociation between ADHD and executive dysfunction, and also the stability of the executive dysfunction over time. Although the Persistent and Remitted ADHD groups differed in adult diagnostic status, the two groups did not differ on any measure of cognitive function. The diagnostic change in the Remitted ADHD group was accompanied by an apparent normalization of positive PCC-MPFC functional connectivity, but the Remitted and Persistent ADHD groups both exhibited similar reductions in negative MPFC-DLPFC functional connectivity. Thus, at both behavioral and brain levels of analysis, it appears that the diagnosis of ADHD is more amenable to adulthood remission than are the executive dysfunctions that may accompany ADHD.

Limitations of Study

A number of limitations of the present study can be noted. First, as is common in psychiatric research, a few participants were on medications. However, all participants refrained from taking their short-acting medications for 24 hours prior to scanning, and the findings were similar when remitted patients taking ADHD medication were excluded from analysis. Second, the focus on the PCC and MPFC based on evidence that these brain regions and their intrinsic connectivity are disrupted in ADHD and other disorders

(Whitfield-Gabrieli *et al.*, 2008; Sheline *et al.*, 2010) leaves similarities and differences between persistent and remitted ADHD in other networks unexamined. Third, the Persistent ADHD group consisted of only 13 patients, which may inflate statistical effects (Button *et al.*, 2013). This concern is mitigated by the fact that the findings in the smallest group in our study are a replication of those reported for 20 other adults with Persistent ADHD (Castellanos *et al.*, 2008). What is most unique in the present study, however, are the differences in the larger and novel sample of 22 patients with Remitted ADHD. Fourth, differences in motion between groups can mask long-range (e.g., PCC-MPFC) and induce short-range correlations between brain regions during the resting-state scan (Power *et al.*, 2012). We employed first-level statistical approaches (i.e., regression of outliers in the global signal intensity and motion) that were intended to account for such confounds. Further, we performed additional analyses with subgroups matched on movement combined with the first-level statistical approach. Fifth, it is difficult to be certain whether impaired scores on some (but not other) measures of executive function in the present ADHD groups are secondary to lower IQ scores, or whether, instead, both lower IQ scores and executive dysfunctions are expressions of a common cognitive impairment.

Summary

We identified circuit-specific differences and similarities in a group of prospectively identified individuals who either remitted or persisted in their ADHD diagnoses in adulthood. The reduced PCC-MPFC functional connectivity in the present study, which was associated with the clinical state of ADHD, may offer an insight into brain mechanisms that are central to the diagnosis of ADHD itself. In contrast, the

reduced negative MPFC-DLPFC correlations may reflect cognitive deficits related to ever having ADHD. The neurobiological dissociation between the PCC-MPFC and MPFC-DLPFC functional connectivities may address the complex relation between the diagnosis of ADHD and the variable status of executive function across patients with a history of ADHD.

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Figure & Figure Legends

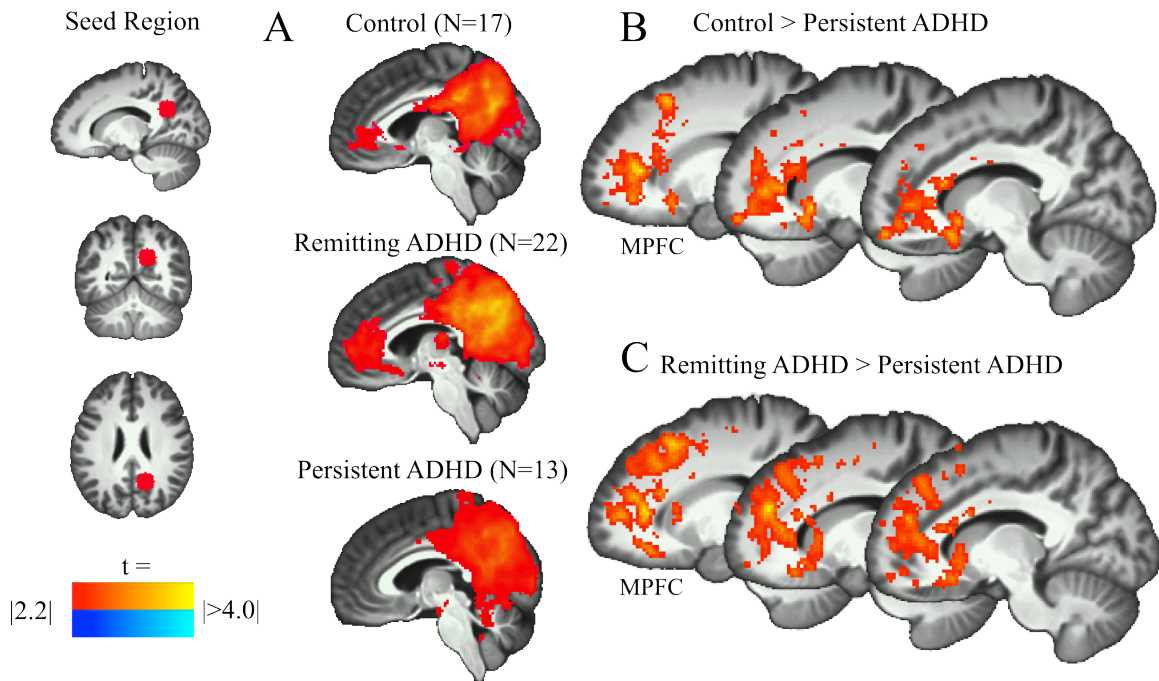


FIGURE 1. (A) One sample t-tests in each group showed positive functional connectivity between the posterior cingulate cortex (PCC) (MNI coordinates: $x = 15, y = -56, z = 28$) and regions of the medial prefrontal cortex (MPFC) in Control and Remitted ADHD groups, but not in Persistent ADHD group. (B) Between-group comparisons revealed greater positive functional connectivity between PCC and MPFC for the Control group than the Persistent ADHD group. (C) The Remitted ADHD group also showed greater positive functional connectivity between the PCC and MPFC than the Persistent ADHD group. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.

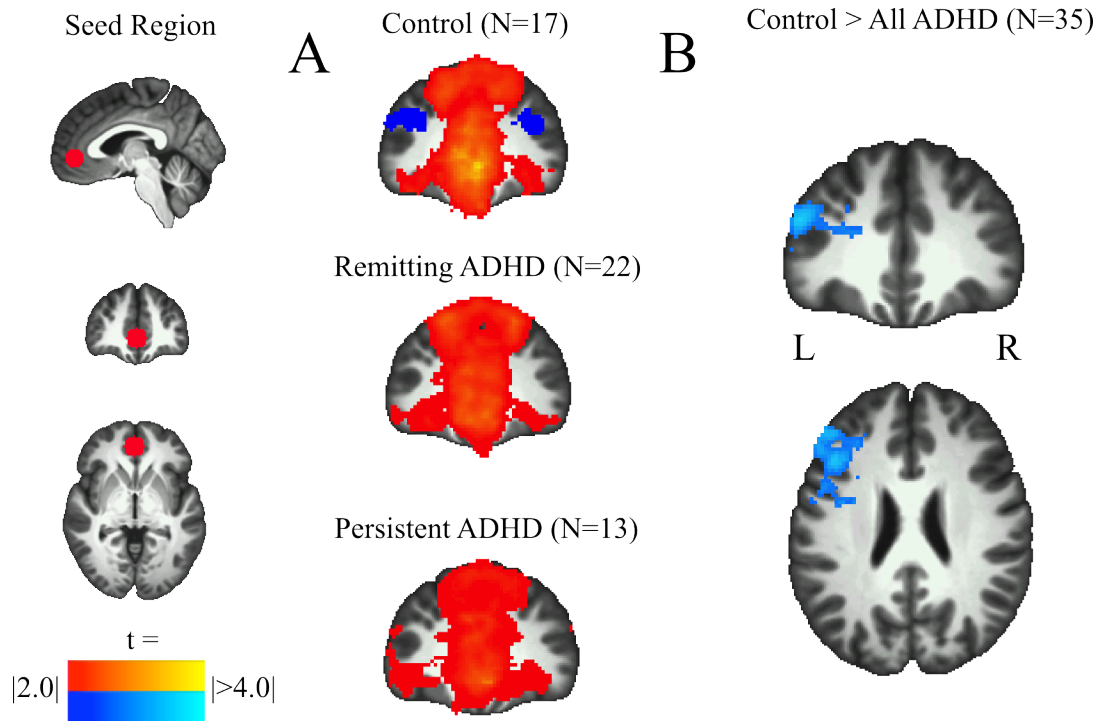


FIGURE 2. (A) One sample t-tests in each group showed negative functional connectivity between the medial prefrontal cortex (MPFC) (MNI coordinates: $x = -1, y = 47, z = -4$) and regions of the dorsolateral prefrontal cortex (DLPFC) in the Control group, but not in either the Remitted or the Persistent ADHD groups. (B) Between-group comparison revealed greater negative functional connectivity between the MPFC and left DLPFC for the Control group compared to all patients with ADHD. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.

Supplementary materials

Materials and methods

Participants

Participants ($n = 54$) were derived from longitudinal case-control family studies of boys and girls 6-17 years of age at baseline assessment, who were ascertained from pediatric and psychiatric sources (Biederman *et al.*, 1992, 1996). Excluded were adopted participants or participants with psychosis, autism, inadequate command of the English language, a Full Scale IQ < 80 , or major sensorimotor disabilities (paralysis, deafness, blindness). All probands in the ADHD groups met DSM-III-R criteria for ADHD at the initial baseline assessment completed in childhood. Participants were previously followed-up at 5 and 11 years after baseline (Biederman *et al.*, 2012a; Mick *et al.*, 2011). Two participants were excluded from final analysis because 1 control participant met diagnostic criteria for ADHD and 1 Persistent ADHD participant had a poorly documented baseline diagnosis (final $n = 52$).

Assessment Procedures

Concurrent Diagnostic Assessment

Psychiatric diagnostic information relied on the Structured Clinical Interview for DSM-IV (SCID) (First and Gibbon, 1997) supplemented with modules from the DSM-IV modified K-Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological Version (K-SADS-E) (Orvaschel and Puig-Antich, 1987) to assess childhood diagnoses, such as ADHD, as well as current symptoms and symptoms since last follow-up.

Interviewers were highly trained psychometricians blind to baseline ascertainment group, ascertainment source, and prior assessments. Kappa coefficients of agreement between

interviewers and board certified child and adult psychiatrists and experienced licensed clinical psychologists were previously reported (median kappa for individual disorders=.98) (Biederman *et al.*, 1992).

The total symptoms of ADHD, based on the structured diagnostic interview, were used to define the current diagnostic status (e.g., persistent versus remitted). Persistence of ADHD was defined as meeting full or subthreshold criteria for DSM-IV ADHD. A subthreshold ADHD case was defined as endorsing more than half but less than full diagnostic criteria (i.e., at least four ADHD symptoms in either the inattentive or the impulsive/hyperactive criteria lists) and meeting all other diagnostic criteria (e.g., age at onset). Participants who qualified for remittance did not meet subthreshold criteria at follow up.

Concurrent Functional Assessment

We used several measures to characterize the functional history and current status of the adult participants. A DSM-IV Global Assessment of Functioning Scale (GAF) score was obtained to assess the overall functioning of each individual at the time of scanning (current), as well as a retrospective assessment across their lifetime (past). Socioeconomic status was measured using the two-factor Hollingshead index (Hollingshead, 1975) (higher score=lower status) composed of educational level (scored 1-7, lower score=higher level) and occupational level (scored 1-9, lower score=higher level). Participants also completed the Social Adjustment Scale (Weissman, 1999) to measure interpersonal functioning, and the Quality of Life Enjoyment and Satisfaction questionnaire (Endicott *et al.*, 1993) to assess the degree of enjoyment and satisfaction experienced in several areas of daily functioning.

Concurrent Neuropsychological Assessment

Participants were administered the Digit Span and Arithmetic subtests from the Working Memory Index and the Digit Symbol subtest from the Processing Speed Index of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) and the Wechsler Abbreviated Intelligence Scale (WASI) (Wechsler, 1999) (scaled scores were analyzed). Executive functions were assessed with the Color-Word Interference (Inhibition) and Trail Making (Number-Letter Switching) subtests from the Delis Kaplan Executive Function System (D-KEFS) (Delis *et al.*, 2001) and the Stockings of Cambridge and the Spatial Working Memory subtests of the Cambridge Neuropsychological Test Assessment Battery (CANTAB) (Sahakian and Owen, 1992). Participants also completed the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) (Roth *et al.*, 2005) an empirically derived self-report assessment of behaviors associated with executive dysfunction.

Behavioral Statistical Analysis

We compared across groups demographic characteristics, clinical variables (i.e., prevalence of lifetime, interval and current psychiatric disorders, current and past GAF scores, lifetime presence of medication), and neuropsychological scores. Tests were performed using the Pearson χ^2 test for categorical data and independent samples t-tests for continuous data. We controlled for any demographic confound that reached significance at the 0.05 alpha level. To reduce the probability of Type I errors when conducting comparisons on psychiatric disorders and neuropsychological testing, we used a corrected alpha equal to 0.01 as the threshold of statistical significance. All tests were two-tailed.

Imaging Procedure

Resting functional MRI scans lasted 6 minutes during which participants were instructed to “keep your eyes open and think of nothing in particular.” Resting scans consisted of 67 interleaved oblique, 2 mm thick axial slices, covering the entire brain (repetition time = 6.0 s, echo time = 30 ms, flip angle = 90°, FOV 128 x 128, resulting in 2 mm isotropic voxels). Prospective acquisition correction (PACE) was used to mitigate artifacts due to head motion (Thesen *et al.*, 2000). T1-weighted whole brain structural images were also acquired (MPRAGE sequence; repetition time = 2530 s, echo time = 3.48 ms, flip angle = 90°, FOV 256 x 256, resulting in 1 mm isotropic voxels).

Data Preprocessing

SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) was used to preprocess fMRI data. Functional images were slice-time and motion corrected, registered to structural scans, normalized to an MNI template, and smoothed with a 6 mm FWHM Gaussian kernel.

Motion Artifact Detection

Prior to spatial filtering, an artifact detection toolbox, ART (http://www.nitrc.org/projects/artifact_detect) was used to identify outlier data points defined as volumes that exceeded 3 z-normalized standard deviations away from mean global brain activation across the entire volume, or a composite movement threshold of 0.5 mm framewise displacement. The composite movement measure was calculated by converting the 3 rotation and 3 translation parameters into parameters reflecting the trajectories of 6 points located on the center of each of the faces of a bounding box around the brain. We then used the maximum scan-to-scan movement of any of these

points as the composite score for each time point and then averaged across time points to calculate a mean composite movement score for the entire scan for each individual participant.

Functional Connectivity Analysis

We used a seed-driven approach with custom software developed in Matlab, “Conn toolbox,” (<http://www.nitrc.org/projects/conn/>), for functional connectivity analyses (Whitfield-Gabrieli and Nieto-Castanon, 2012). Resting-state functional data were temporally band-pass filtered (0.009 Hz to 0.08 Hz). Head motion parameters (3 rotation, 3 translation), as well as their first derivatives, and outlier nuisance regressors (one for each motion outlier consisting of all zeros and a 1 at the respective outlier time point) were regressed out of the first level GLMs. Spurious sources of non-neuronal noise were accounted for through an anatomical component based (aCompCor) approach (Behzadi *et al.*, 2007). Each participant’s structural image was segmented into white matter (WM), gray matter (GM), and cerebral spinal fluid (CSF) using SPM8. WM and CSF masks were eroded by one voxel to avoid partial volume effects with adjacent gray matter. The first 3 principal components of the signals from the eroded WM and CSF noise ROIs were removed with regression.

Pearson’s correlation coefficients were calculated between the seed time-series and the time course of all other voxels. The resulting Pearson’s correlation coefficients were z-transformed using the Fisher transformation to conform to the assumptions of the General Linear Model (normally distributed) for second-level analyses.

A priori seeds were the two major midline nodes of the DMN, the posterior cingulate cortex and the medial prefrontal cortex. The PCC seed was defined following a

study of resting-state functional connectivity in ADHD (Castellanos *et al.*, 2008) as a 10 mm sphere around the coordinates: $x = 15, y = -56, z = 28$, in Montreal Neurological Institute (MNI) space. The MPFC seed was defined following the literature (Fox *et al.*, 2005) as a 10 mm sphere around the MNI coordinates: $x = -1, y = 47, z = -4$.

Neuroimaging Statistical Analysis

Neuroimaging statistical analyses utilized a statistical height threshold of $P < 0.05$ and Familywise Error (FWE) correction ($P < 0.05$) at the cluster level to identify significant clusters in all comparisons. We used two-tailed one sample t-tests to compare each group's PCC seed and MPFC seed whole-brain correlations to baseline. To evaluate the *a priori* hypotheses that ADHD groups would show reduced positive correlations between the PCC seed and MPFC region and reduced negative correlations between the MPFC seed and DLPFC region, we used one-tailed independent samples t-tests. The *a priori* hypotheses were based on (1) previous findings in adults (Castellanos *et al.*, 2008) and children (Fair *et al.*, 2010) with ADHD showing reduced positive correlation between the PCC and MPFC relative to age-matched controls, and (2) reduced negative correlations between the MPFC and DLPFC observed in neuropsychiatric groups with executive function deficits compared to controls (Schizophrenia: Whitfield-Gabrieli *et al.*, 2009; Depression: Sheline *et al.*, 2010).

Groups Matched On Motion

Movement during resting state scans is a major concern, artificially inducing short-range and masking long-range correlations (Power *et al.*, 2012). This can be especially problematic when investigating patient populations (Fair *et al.*, 2013). To address this potential confound, in addition to regressing out time points that either exceeded 0.5 mm

framewise displacement or 3 z-normalized standard deviations of the mean intensity threshold identified by our motion artifact detection software at the first level (see the sections above), we also reran the same analyses removing four participants with excessive movement (greater than 10% of time points flagged as outliers). This resulted in final groups of 17 control participants, 10 ADHD participants who met persistent criteria, and 21 ADHD participants who met remitted criteria. The final groups did not differ significantly from one another in amount of composite movement.

Results

Demographic and Clinical Variables

Controls ($n = 17$), Remitted ADHD ($n = 22$), and Persistent ADHD ($n = 13$) groups did not differ on demographic variables, including age at baseline or at the time of the current assessment (Supplementary Table 1). The two ADHD groups did not differ in ADHD severity (number of symptoms) at childhood diagnosis. The three groups were also similar on socioeconomic and social adjustment scales. However, Controls showed a statistically significant higher quality of life measure when compared to Persistent ADHD. Participants with Remitted and Persistent ADHD had significantly worse past GAF scores than Controls, while only Persistent ADHD had significantly worse current GAF scores when compared to Controls. Remitted and Persistent ADHD had a similar history of medication treatment. At the time of the study, 5 Persistent and 4 Remitted ADHD participants were taking stimulant ADHD medications. No participants had taken ADHD medications in the 24 hours preceding the scan. All analyses were re-run removing the 4 Remitted ADHD participants taking ADHD medications resulting in the same outcomes (Supplementary Fig. 1 and 2). Thus, to maintain a larger sample size we

report below the analyses performed with the 4 Remitted ADHD participants included. There were no differences between the ADHD groups in the rates of current comorbidities or comorbidities between the last follow-up and current follow-up at a corrected alpha of 0.01 (Supplementary Table 2).

Neuropsychological Results

Compared to the Control Group, both Remitted and Persistent ADHD groups had lower WASI Full IQs, higher (worse) BRIEF-A scores, and lower CANTAB – Spatial Working memory performance. However, the Control group did not differ significantly from the Persistent ADHD group in Spatial Working Memory performance at the more stringent alpha (0.01) used to correct for multiple comparisons. Compared to the Control group, the Remitted ADHD group performed significantly worse on the Arithmetic and Digit Symbol WAIS III/WISC IV subtests.

Neuroimaging Results

Motion

The Control and Remitted ADHD groups did not differ significantly in movement ($t_{37} = 0.60, P = 0.51$). In contrast, the Persistent ADHD group moved significantly more than the Control group ($t_{28} = 2.62, P = 0.01$) and tended to move more than the Remitted group ($t_{33} = 1.81, P = 0.07$). When participants were removed from analyses for more than 10% of time points being flagged with excessive movement (> 0.5 mm), relative to the previous time point, the groups no longer differed significantly in their amounts of motion (all P 's > 0.1) (Supplementary Table 3).

Discussion

Network Specific Developmental Trajectories

ADHD is a neurodevelopmental disorder, and the two circuits examined in the present study may have different developmental trajectories. The PCC-MPFC correlation has a very modest growth in development from ages 8-24 once motion and other sources of artifact are controlled (Satterthwaite *et al.*, 2013; Chai *et al.*, 2013). Conversely, the MPFC-DLPFC anticorrelation exhibits a large developmental change, reversing from a positive correlation in children ages 8-12 to a negative correlation in adolescents and adults (Chai *et al.*, 2013). Future research may indicate how the different developmental trajectories of the two circuits are related to different aspects of ADHD. For example, it is possible that a longer developmental trajectory makes a circuit more vulnerable through development and less plastic in adulthood.

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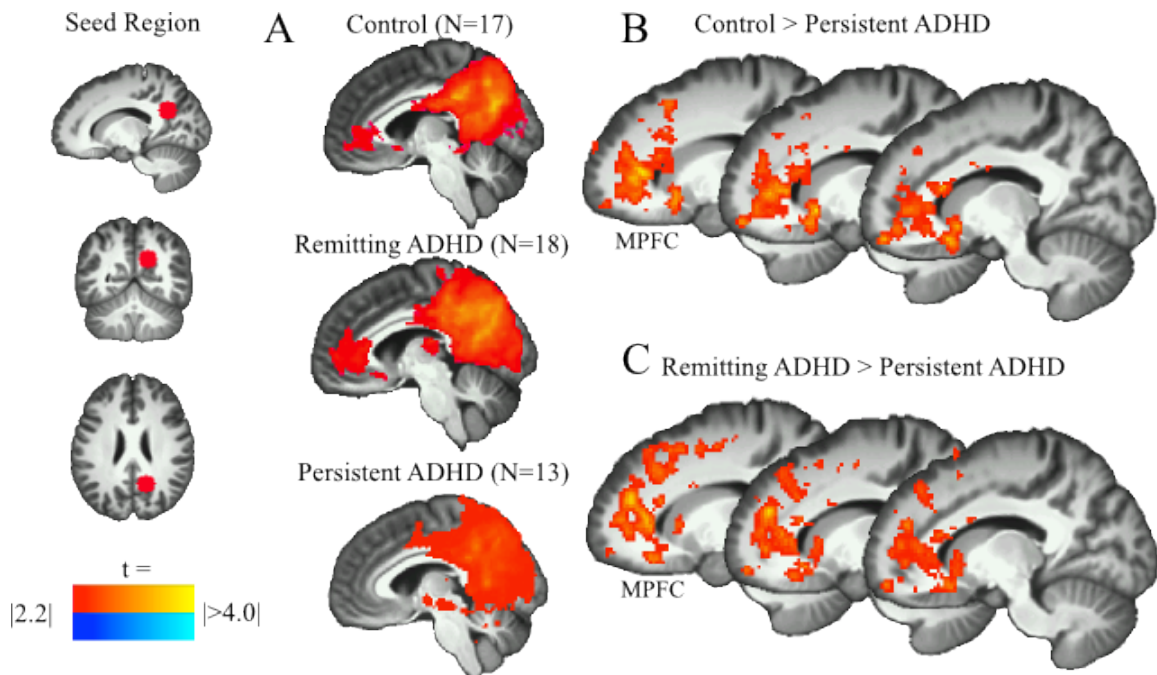
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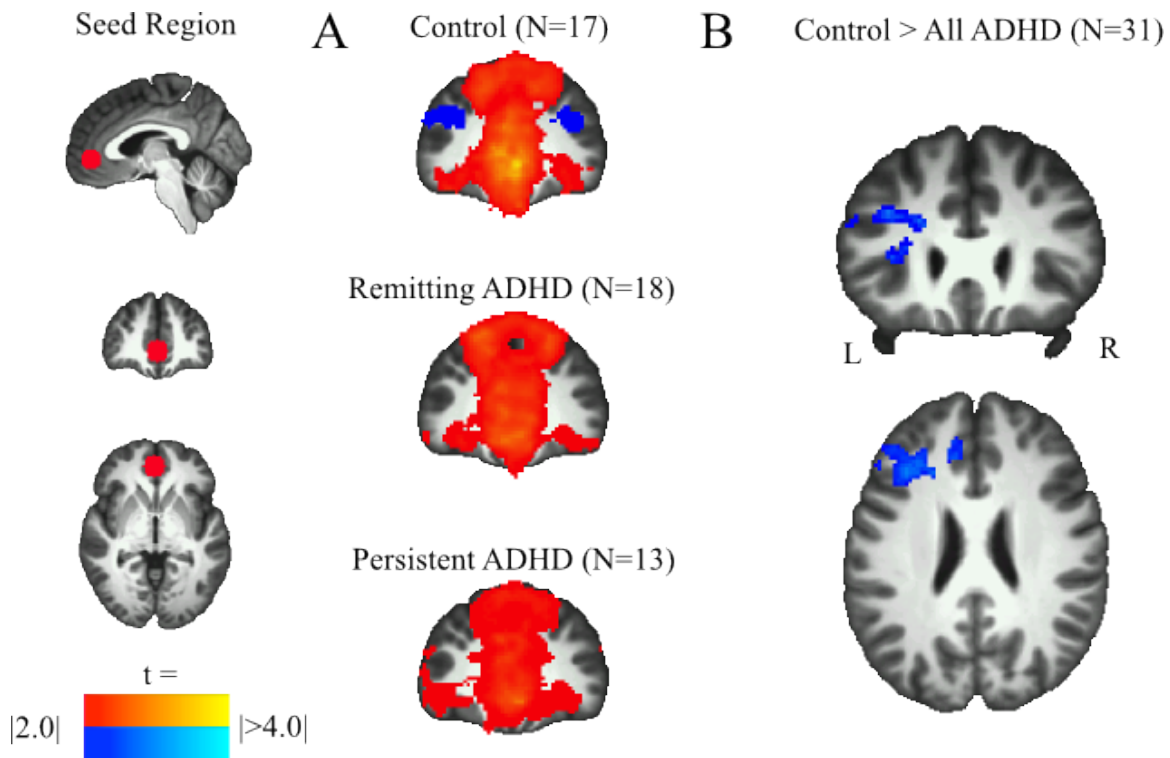
Supplementary Figure Legends



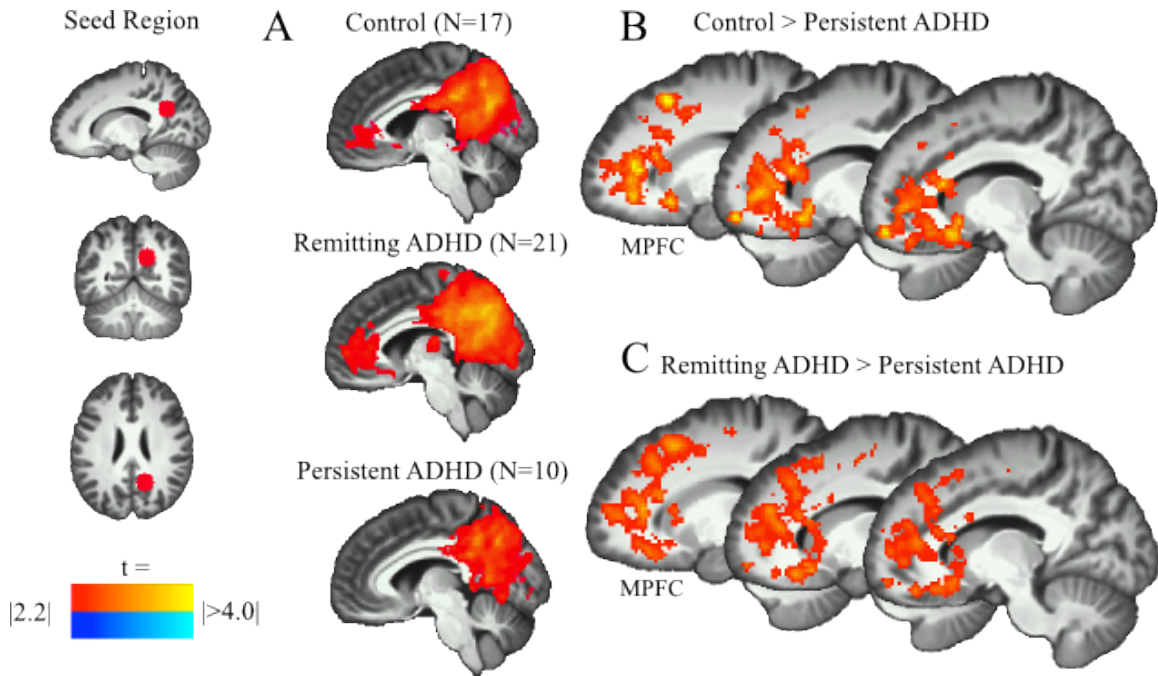
Supplementary Figure 1 PCC seed group comparisons when removing Remitted

ADHD participants who were taking ADHD medications at follow-up (A) One

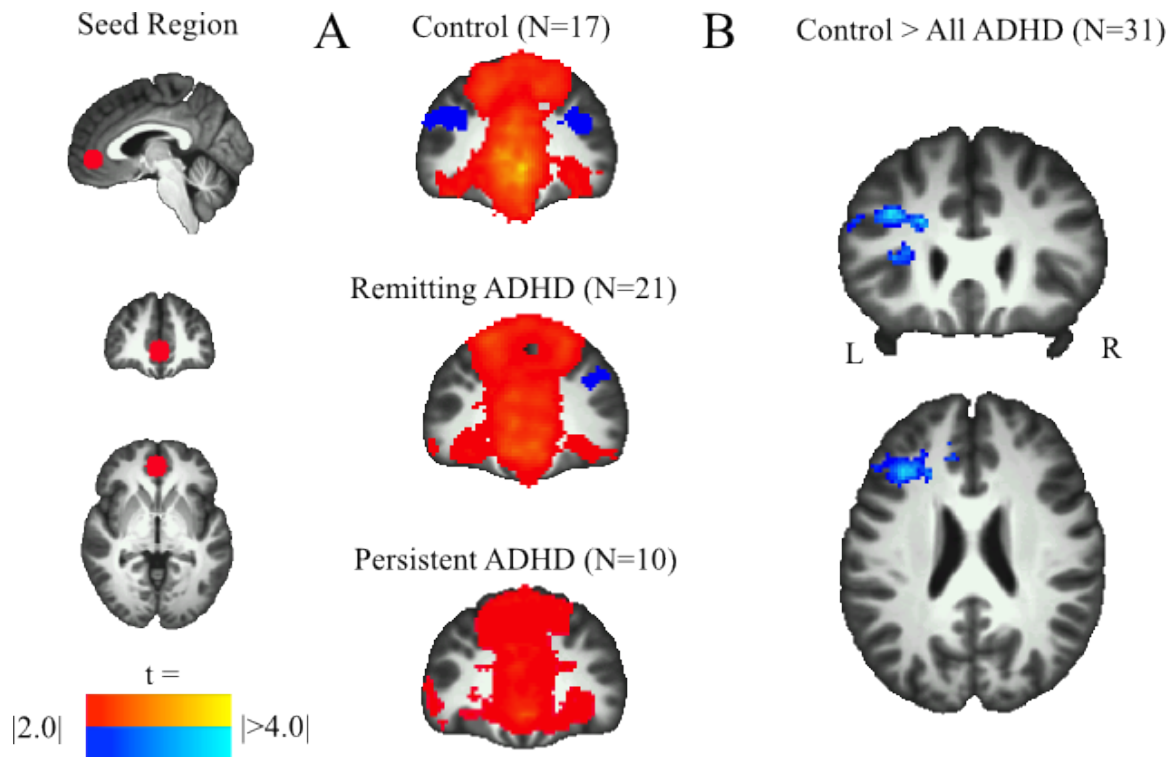
sample t-tests versus baseline showed positive functional connectivity between the posterior cingulate cortex (PCC) (MNI coordinates: $x = 15, y = -56, z = 28$) and regions of the medial prefrontal cortex (MPFC) in Control and Remitting ADHD groups, but not in Persistent ADHD group. (B) Comparisons between Control and Persistent ADHD revealed greater positive functional connectivity between PCC-MPFC for Control compared to Persistent ADHD groups. (C) A similar comparison between Remitted ADHD and Persistent ADHD also showed greater positive functional connectivity between the PCC-MPFC in the Remitted ADHD group than the Persistent ADHD group. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.



Supplementary Figure 2 MPFC seed group comparisons when removing Remitted ADHD participants who were taking ADHD medications at follow-up (A) Following one sample t-tests versus baseline in each group only the Control group showed negative functional connectivity between the medial prefrontal cortex (MPFC) (MNI coordinates: $x = -1, y = 47, z = -4$) and the bilateral dorsolateral prefrontal cortex (DLPFC). **(B)** Comparison between the Control group and all participants with ADHD (Remitted and Persistent combined) showed that the Control group had greater negative functional connectivity between MPFC and left DLPFC than all patients with ADHD. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.



Supplementary Figure 3 PCC seed group comparisons when matching groups on motion (A) One sample t-tests in each group showed positive functional connectivity between the posterior cingulate cortex (PCC) (MNI coordinates: $x = 15, y = -56, z = 28$) and regions of the medial prefrontal cortex (MPFC) in Control and Remitting ADHD groups, but not in Persistent ADHD group. **(B)** Between-group comparisons revealed greater positive functional connectivity between PCC and MPFC for Control compared to Persistent ADHD groups. **(C)** Remitted ADHD group also showed greater positive functional connectivity between the PCC and MPFC than Persistent ADHD group. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.



Supplementary Figure 4 MPFC seed group comparisons when matching groups on motion (A) One sample t-tests in each group showed negative functional connectivity between the medial prefrontal cortex (MPFC) (MNI coordinates: $x = -1, y = 47, z = -4$) and regions of the dorsolateral prefrontal cortex (DLPFC) in the Control group bilaterally and the Remitted ADHD group in the right hemisphere, but not in the Persistent ADHD group. **(B)** Between-group comparison revealed greater negative functional connectivity between MPFC and left DLPFC for Control compared to all patients with ADHD. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.

Supplementary Tables

Supplementary Table 1. Sociodemographic and Clinical Characteristics

	Controls N (%) Mean±SD	Remitted ADHD N (%) Mean±SD	Persistent ADHD N (%) Mean±SD
AGE			
Baseline	10.1±3.0	10.8±3.2	9.9±3.4
Current	28.7±4.0	28.2±5.9	28.7±5.2
SYMPTOMS			
Baseline (DSM-III)	1.1±1.2 ^{a***,b***}	10.7±2.1	11.1±2.6
Current (DSM-IV)	0.3±1.4 ^{a**,b***}	1.7±1.9 ^{b***}	7.8±2.3
Male	11 (65)	10 (45)	7 (53)
Caucasian	17 (100)	22 (100)	13 (100)
Socioeconomic status	1.8±0.5	1.7±0.8	2.1±0.8
Quality of Life	57.6±6.5 ^{b**}	53.5±9.5	50.5±5.3
Social Adjustment Scale	1.7±0.4	1.9±0.6	1.9±0.4
Current Global Assessment of Function (GAF)	68.1±5.5 ^{b*}	64.4±6.8	63.3±4.9
Past GAF	65.2±8.7 ^{a**,b**}	58.2±8.1	52.3±8.6
TREATMENT HISTORY			
Medication for ADHD	0 (0) ^{a***,b***}	19 (86)	13 (100)

^a vs. R-ADHD

^b vs. P-ADHD

*p<0.05, **p<0.01, ***p<0.001

Supplementary Table 2. Since Last Follow-up and Current Comorbidities

	Controls	Remitted ADHD	Persistent ADHD
	N (%)	N (%)	N (%)
Major Depression Disorder			
% Since Last Follow-up	1 (6)	7 (32)	5 (38) ^{a*}
% Current	0 (0)	2 (9)	1 (7)
Bipolar Disorder			
% Since Last Follow-up	0 (0)	1 (4)	2 (15)
% Current	0 (0)	1 (4)	1 (7)
Multiple (>2) Anxiety Disorders			
% Since Last Follow-up	0 (0)	2 (9)	1 (7)
% Current	0 (0)	1 (4)	1 (7)
Substance or Alcohol Abuse and/or Dependence			
% Since Last Follow-up	6 (35)	5 (22)	6 (46)
% Current	2 (11)	3 (13)	0 (0)
Smoking			
% Since Last Follow-up	1 (6)	5 (22)	2 (15)
% Current	1 (6)	3 (13)	1 (7)
Oppositional Defiant Disorder			
% Since Last Follow-up	0 (0)	4 (18)	3 (23)
% Current	0 (0)	2 (9)	1 (7)
Antisocial Personality Disorder			
% Since Last Follow-up	1 (6)	2 (9)	1 (7)
% Current	0 (0)	1 (4)	0 (0)
Tourette's and/or Tic Disorder			
% Since Last Follow-up	0 (0)	1 (4)	3 (23) ^{a*}
% Current	0 (0)	0 (0)	2 (15) ^{a*}

^a vs. R-ADHD
^b vs. P-ADHD
*p<0.05, **p<0.01, ***p<0.001

Supplementary Table 3. Neuropsychological Measures

	Controls	Remitted ADHD	Persistent ADHD
	Mean±SD	Mean±SD	Mean±SD
BRIEF Total Score	43.9±5.5 ^{a*b***}	55.0±11.0	60.9±7.2
CANTAB			
Stockings of Cambridge	0.74±0.8	0.32±1.4	0.38±1.0
Spatial Working Memory	0.80±0.5 ^{a**b*}	0.01±1.0	0.08±0.9
WAIS III/WISC IV			
Digit Span	11.41±2.4	10.9±2.3	12±3.1
Arithmetic	12.76±1.6 ^{a**}	10.4±2.4	11.5±2.7
Digit Symbol	12.6±2.9 ^{a**}	9.64±2.2	10.8±2.6
WASI			
Full IQ	120±7.5 ^{a**b***}	108.9±12.2	109.7±7.2
D-KEFS			
Color-Word Inhibition	12.0±3.9	10.6±3.3	10.8±3.0
Color-Word Switching	11.5±2.6	9.9±3.4	10.6±2.0
Trails – Number-Letter Switching	11.4±2.2	10.3±2.2	11.7±1.7

^a vs. R-ADHD
^b vs. P-ADHD
*p<0.05, **p<0.01, ***p<0.001

Supplementary Table 4. Summary of Movement Across Groups

Unmatched	Controls (n=17)	Remitted ADHD (n=22)	Persistent ADHD (n=13)	Test Statistic
Composite	Mean±SD 0.35±0.20	Mean±SD 0.39±0.26	Mean±SD 0.54±0.17	^a $t_{37}=0.61$, $p=0.61$ ^b $t_{28}=2.62$, $p=0.01$ ^c $t_{33}=1.81$, $p=0.07$
Matched	Controls (n=17)	Remitted ADHD (n=21)	Persistent ADHD (n=10)	
Composite	Mean±SD 0.35±0.20	Mean±SD 0.35±0.20	Mean±SD 0.47±0.13	^a $t_{36}=0.05$, $p=0.95$ ^b $t_{25}=1.63$, $p=0.11$ ^c $t_{29}=1.63$, $p=0.11$
^a CONTROL vs. R-ADHD ^b CONTROL vs. P-ADHD ^c R-ADHD vs. P-ADHD				