

REPORT**Brain differences between persistent and remitted attention deficit hyperactivity disorder****Aaron T. Mattfeld,^{1,2} John D. E. Gabrieli,^{1,2} Joseph Biederman,^{3,4} Thomas Spencer,^{3,4} Ariel Brown,^{3,4} Amelia Kotte,^{3,4,5} Elana Kagan^{3,4} and Susan Whitfield-Gabrieli^{1,2}**

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Previous 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.

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

Abbreviations: ADHD = attention deficit hyperactivity disorder; DMN = default mode network

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 (Visser *et al.*, 2014). 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). Although 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 patients with ADHD 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: (i) patients with persistent ADHD diagnoses in both childhood and adulthood; (ii) patients with remitted ADHD who had met the diagnoses in childhood but no longer met that diagnosis in adulthood; and (iii) control participants documented as not having ADHD in either childhood or adulthood.

We used functional MRI 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; Uddin *et al.*, 2008; Fair *et al.*, 2010). Resting-state functional MRI is a useful method for studying the pathophysiology of neurodevelopmental disorders because it can be obtained over a short period of time (~6 min) (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 functional MRI assesses the correlation of blood oxygen level-dependent 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 (anti-correlations) with other brain regions that are activated for executive function (task-positive networks), such as the dorsolateral prefrontal cortex (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 anti-correlations between DMN and task-positive networks. We examined two major nodes of the DMN, the posterior cingulate cortex and medial prefrontal cortex, which have previously shown to be functionally hypoconnected in adults with ADHD (Castellanos *et al.*, 2008). We measured whole-brain positive correlations with the posterior cingulate cortex region in order to compare functional connectivity within the DMN across groups (Castellanos *et al.*, 2008). We also measured negative correlations with the medial prefrontal cortex region to compare functional connectivity between the DMN and a brain region associated with executive function, the dorsolateral prefrontal cortex (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 Supplementary material. The current neuroimaging wave occurred ~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 participants with ADHD who met persistent criteria, and 22 participants with ADHD 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 T Siemens Trio scanner using a 32-channel head coil. Standard preprocessing and seed-based functional connectivity analyses were performed combined with stringent motion artefact correction procedures (see Supplementary material 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 differently 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 material for a detailed description of the behavioural results.

Neuroimaging results

Posterior cingulate cortex seed

The control [Fisher's $z = 0.15$, standard deviation (SD) = 0.13] and remitted ADHD (Fisher's $z = 0.17$, SD = 0.12) groups exhibited positive correlations between the posterior cingulate cortex and medial prefrontal cortex. In contrast, there was not a significant posterior cingulate cortex–medial prefrontal cortex positive correlation in the persistent ADHD group (Fig. 1A). Statistical tests between groups revealed significant reductions in posterior cingulate cortex–medial prefrontal cortex 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

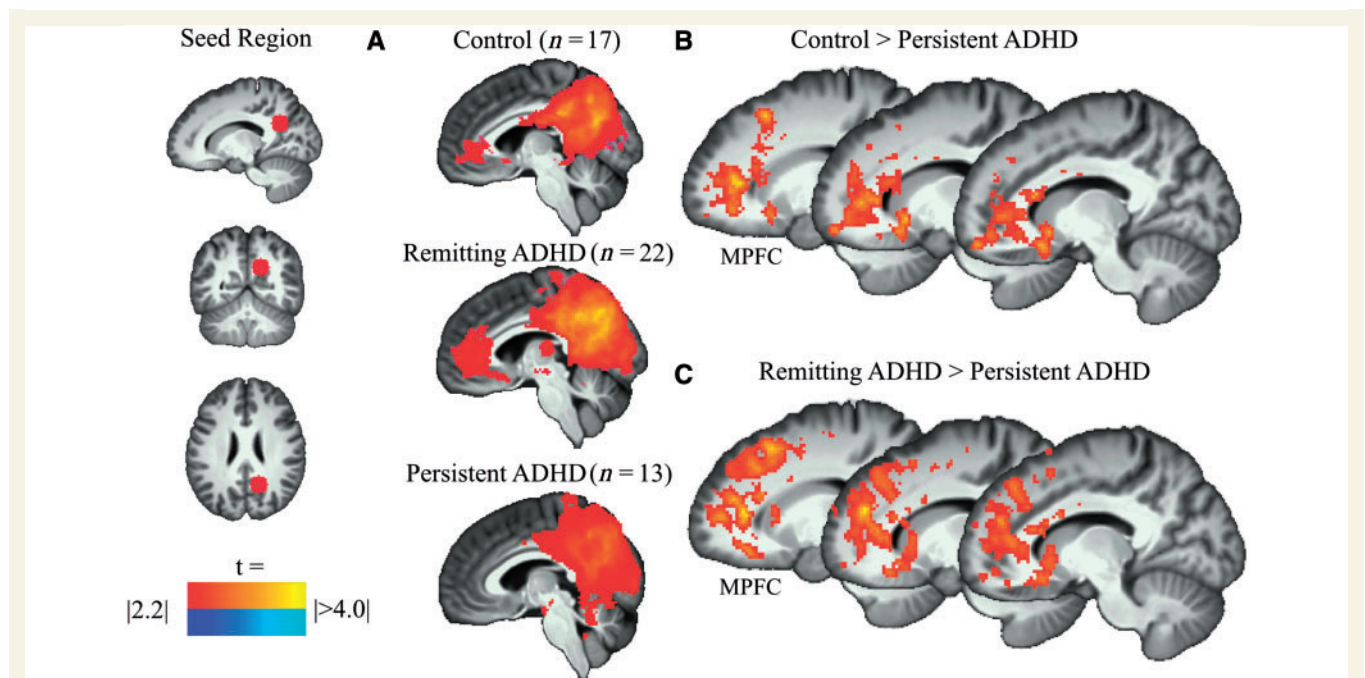


Figure 1 (A) One sample t -tests in each group showed positive functional connectivity between the posterior cingulate cortex (MNI coordinates: $x = 15, y = -56, z = 28$) and regions of the medial prefrontal cortex (MPFC) in control and remitted ADHD groups, but not in the persistent ADHD group. (B)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

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).

Medial prefrontal cortex seed

The control group exhibited significant negative correlations between the medial prefrontal cortex and bilateral dorsolateral prefrontal cortex (Fisher's $z = -0.12$, $SD = 0.16$) (Fig. 2A). There were no significant negative correlations between the medial prefrontal cortex and dorsolateral prefrontal cortex for either the remitted or persistent ADHD groups. When directly comparing whole-brain correlations of the medial prefrontal cortex seed in the remitted and persistent groups we did not observe significant differences in the dorsolateral prefrontal cortex. Therefore, both groups were collapsed into a single group (all ADHD, $n = 35$) for subsequent medial prefrontal cortex seed between-group comparisons. The ADHD group had significantly reduced negative correlations between the medial prefrontal cortex and left dorsolateral prefrontal cortex compared to the control group (Fig. 2B). At a slightly more liberal threshold [uncorrected $P < 0.07$, family-wise error (FWE) cluster level correction $P < 0.05$], a similarly reduced negative correlation between the medial prefrontal cortex and right dorsolateral prefrontal cortex 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 dorsolateral prefrontal cortex. Similar differences between

medial prefrontal cortex and left dorsolateral prefrontal cortex 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 dorsolateral prefrontal cortex.

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 posterior cingulate cortex–medial prefrontal cortex 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 medial–dorsolateral prefrontal cortex anti-correlation was related to childhood diagnosis of ADHD independent of adult diagnostic status. Both ADHD groups exhibited reduced negative medial–dorsolateral prefrontal cortex connectivity relative to the control group, and the persistent and remitted ADHD groups did not differ from one another.

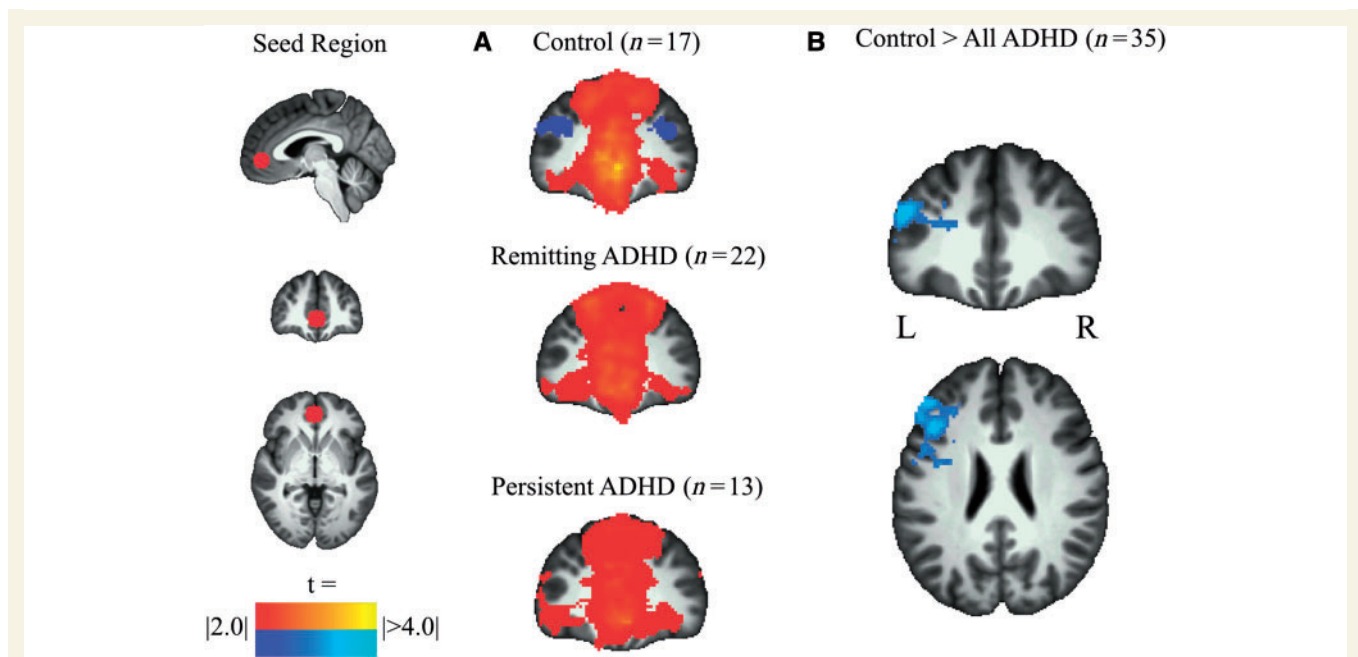


Figure 2 (A) One sample t -tests in each group showed negative functional connectivity between the medial prefrontal cortex (MNI coordinates: $x = -1, y = 47, z = -4$) and regions of the dorsolateral prefrontal cortex in the control group, but not in either the remitted or the persistent ADHD groups.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

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 patients with ADHD 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 seemed 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 posterior cingulate cortex and medial prefrontal cortex, two major midline nodes of the DMN. A previous study examining ADHD adults of a similar age range, by definition cases of persistent ADHD, discovered decreased

posterior cingulate cortex–medial prefrontal cortex 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 syndromic continuity between paediatric (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 (Schulz *et al.*, 2005; Schneider *et al.*, 2010).

Brain similarities between persistent and remitted groups

Altered functional connectivity between medial and dorsolateral prefrontal cortex appeared to reflect ever having been diagnosed with ADHD, irrespective of current diagnostic state. The control group exhibited significant anti-correlations between medial and dorsolateral prefrontal cortex, whereas neither the remitted nor the persistent groups exhibited an anti-correlation, and the control group exhibited significantly greater left medial–dorsolateral prefrontal cortex anti-correlation than the combined ADHD groups. Greater negative correlation between the medial and dorsolateral prefrontal cortex, 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 medial–dorsolateral prefrontal cortex anti-correlation 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 highlight emerging views on the relationship between ADHD and executive functions. Although ADHD has been associated with impairments in executive functions (Barkley, 1997), recent evidence indicates a variable relationship between ADHD and executive functions (Castellanos *et al.*, 2006). For example, there is variability among patients with ADHD as to which specific kinds of executive functions are impaired (e.g. inhibitory control versus 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 50–70% of patients with ADHD 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 patients with ADHD 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 posterior cingulate cortex–medial prefrontal cortex functional connectivity, but the remitted and persistent ADHD groups both exhibited similar reductions in negative medial–dorsolateral prefrontal cortex functional connectivity. Thus, at both behavioural and brain levels of analysis, it seems 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, some of the participants

were on medications. However, all participants refrained from taking their short-acting medications for 24 h before scanning, and the findings were similar when remitted patients taking ADHD medication were excluded from analysis. Second, the focus on the posterior cingulate cortex and medial prefrontal cortex based on evidence that these brain regions and their intrinsic connectivity are disrupted in ADHD and other disorders (Whitfield-Gabrieli *et al.*, 2009; 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. posterior cingulate cortex–medial prefrontal cortex) and induce short-range correlations between brain regions during the resting state scan (Power *et al.*, 2012). We used 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.

Conclusion

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 posterior cingulate cortex–medial prefrontal cortex 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 medial–dorsolateral prefrontal cortex correlations may reflect cognitive deficits related to ever having ADHD. The neurobiological dissociation between the posterior cingulate cortex–medial prefrontal cortex and medial–dorsolateral prefrontal cortex 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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Supplementary material

Supplementary material is available at *Brain* online.

Conflict of interest

A full conflict of interest statement is available in the Supplementary material at *Brain* online.

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