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Sex differences in the functional neuroanatomy of working memory in adults with ADHD

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Abstract

Objective—Although attention-deficit/hyperactivity disorder (ADHD) in adults is associated with significant morbidity and dysfunction and afflicts both sexes, relatively few imaging studies have examined females and none have had sufficient power to adequately examine sex differences. We sought to examine sex differences in neural functioning of ADHD adults during performance on a verbal working memory task.

Method—Participants were 44 adults with ADHD matched on age, sex, and estimated IQ to 49 controls. Accuracy and reaction time on an n-back task were measures of working memory performance. The blood-oxygenation-level dependent functional magnetic resonance imaging response was used as a measure of neural activity.

Results—A group by sex ANOVA showed no between-group differences in either reaction time or percent correct for the working memory task. For imaging data, with both sexes combined, ADHD adults showed less activity than controls in prefrontal regions. However, sex-by-group analyses revealed an interaction, such that male ADHD adults showed significantly less activity lateralized to right frontal, temporal and subcortical regions, as well as left occipital and cerebellar regions relative to male controls, whereas female ADHD adults showed no differences from female controls. Exploratory correlation analyses revealed negative associations between working memory related activation and number of hyperactive symptoms for males and number of inattentive symptoms for females.

Conclusions—Male but not female adults with ADHD showed significantly altered patterns of neural activity during performance on a verbal working memory task. Males and females showed different associations between neural activity and ADHD symptoms.

Keywords

ADHD; fMRI; sex differences; working memory; cerebellum; frontal cortex

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by age inappropriate symptoms of inattention, and/or hyperactivity or impulsivity, and is estimated to affect approximately 5% of adults (1,2). Adults with ADHD show more psychiatric comorbidities and impairments in psychosocial, educational, neurocognitive, and occupational functioning than healthy controls (3).

Most ADHD research, including structural and functional neuroimaging, has used males. A recent meta-analysis (4) of s*tructural* imaging studies of ADHD showed that over 80% of the subjects were male and approximately 50% of the studies used 100% male samples. A review of the *functional* imaging literature showed that most studies included either all male (5,6) or mostly male (7) samples. In a meta-analysis of 16 functional imaging studies (8), 10 ADHD samples were 100% male and four were mostly male. In contrast to the large number of all male imaging studies, we found only one structural imaging paper (9) and two functional imaging papers solely studying females (10,11). Clinically, males with ADHD are more likely to have comorbid learning disabilities, disruptive behavior, social dysfunction, and depression, whereas females have an increased rate of substance use disorders and are twice as likely to have the inattentive subtype of the disorder (12). Given these differences in clinical phenomenology, the limited neuroimaging data on females is

problematic, in part because we do not know whether what has been discovered for males will also apply to females.

Findings based on males do not necessarily generalize to females possibly due to sexual dimorphisms observed in the "normal" brain (13,14). For example, it has been suggested that greater bilateral function of the female brain may be protective for certain neurological insults (15). Thus, understanding sex differences in psychiatric disorders could have significant implications (e.g., treatment; 15). With increasing recognition that ADHD occurs in females across the lifespan (16) and that adult rates are more comparable for men and women (i.e., 1.5:1;17) than they are for boys and girls, it is critical that female samples be well represented and that effects of sex be carefully examined. To help address this issue, we conducted a functional imaging study with ADHD adults of both sexes.

In the ADHD functional imaging literature, there are only a few studies that discuss potential effects of sex and/or use enough females to sufficiently analyze female data. A PET study of ADHD adolescents (18) suggested sex differences in the cerebral metabolic rate of glucose when it showed ADHD females had lower glucose metabolism rates than control females and ADHD males. However, this result from a small sample (Ns=5/6) was not replicated in an expanded sample with nearly twice as many females (10). Sheridan and colleagues (11) used functional magnetic resonance imaging (fMRI) to study prefrontal cortex function during working memory performance in adolescent girls with and without ADHD and found no between group differences in neural activation. In contrast, a recent meta-analysis (8) of ADHD functional imaging studies, which included mostly male samples, found activation differences between ADHD and controls in several brain regions, with some of the most robust differences in frontal areas. This suggests that the effects of ADHD in prefrontal and possibly other brain regions may be different for females and males.

In a previous report, we used an n-back task with fMRI to examine the neural underpinnings of working memory in ADHD (19). We found that, relative to controls, ADHD adults showed less activation in cerebellar and occipital regions with a trend towards less activation in the right prefrontal cortex. We have since expanded that sample substantially to examine sex effects.

Theories of ADHD pathophysiology postulate abnormalities in the right prefrontal cortex (20) including frontal hypofunction (8) and right frontal-striatal-cerebellar abnormalities (21). Based on such theories and our previous findings (19), we predicted hypoactivity for ADHD relative to control adults in right frontal and (contralaterally connected) left cerebellar regions for the entire ADHD group. We also predicted that these functional differences would be smaller for females with ADHD than for males based on the absence of significant functional hypoactivity in ADHD females relative to control females (10,11) in contrast to a number of reports of hypoactivity shown in male or mostly male ADHD groups relative to control males in studies with nearly equivalent or smaller samples (5,22). We also conducted exploratory analyses to assess the correlation between ADHD symptoms and neural activation associated with performance on the working memory task for males and females separately.

Method

Participants

Subjects were 44 adults with ADHD and 49 controls comparable on age, sex, handedness, and estimated IQ. Of these 93 subjects, 19 with ADHD and 13 controls (34%) were included in a preliminary report (19). These subjects are part of a larger fMRI study that recruited

subjects from studies of ADHD conducted at Massachusetts General Hospital and from advertisements posted in the Boston area. Written informed consent was obtained for all subjects. The study was approved by the Partners Human Research IRB committee.

We excluded subjects if they: 1) were younger than 18 or older than 55; had 2) an estimated Full Scale IQ < 80; 3) current psychotic disorder; 4) current alcohol or substance abuse or dependence, or chronic histories of abuse or dependence as defined by clinician review of the Structured Clinical Interview for DSM-IV (SCID-I; 23); 5) an inadequate command of English; 6) sensorimotor handicaps or neurological disorders; 7) contraindications to MRI; or 8) were currently taking psychotropic medications. Twenty-seven of the 44 ADHD participants were prescribed psychostimulants in their lifetime: 9 in the past, and 18 currently who underwent a 24-hour washout period before scanning.

ADHD and control adults received identical assessments (consistent with numerous previous studies from this lab e.g., 19). To assess psychopathology we administered the SCID-I (23). To assess ADHD, we used a module derived from the Schedule of Affective Disorders and Schizophrenia for School Age Children (Kiddie SADS-E;24). This module systematically acquires information on all DSM-IV ADHD symptoms, measures and domains of impairment, and age of onset. Previous work shows that retrospective childhood diagnoses of ADHD can be made in a reliable and valid manner using this method (25,26). We considered a subject positive for ADHD if DSM-IV diagnostic criteria were met in childhood and persisted into adulthood. At the time of the clinical interview, there were 13 combined (46% male), 17 inattentive (65% male), 1 hyperactive/impulsive (female), and 13 ADHD-NOS (46% male) subjects. The ADHD-NOS subjects missed the DSM-IV symptom threshold at the time of the interview but otherwise met criteria.

To assess current depression and anxiety we administered the Profile of Mood States (POMS;27) on the day of the scan (See Supplemental Data for details.). Cognitive testing included subtests from the Wechsler Adult Intelligence Scale-III (WAIS-3;28).

Working Memory and Control Tasks for fMRI

We used a block design 2-back variant of the sequential letter, visual “n-back” task (29) that has been used and described by us in previous neuroimaging studies (e.g., 19; See Supplemental Data). Briefly, in the vigilance control “X-task”, the letter “X” was the target. In the working memory 2-back task, a letter was a target if it was the same as the letter that was presented two trials (i.e., letters) previously or “2-back.”

Demographic and Behavioral Data Analysis

2 × 2 ANOVAs with group (ADHD-vs-controls) and sex as factors were run on demographic variables and task performance.

fMRI Data Acquisition and Analysis

Imaging was performed on a Siemens Sonata 1.5 Tesla full-body MR scanner. fMRI was performed using a gradient-echo EPI pulse sequence (21 axial slices, TR=2000 ms, 5-mm thick, 1-mm interslice interval, TE=40 ms, flip angle=90°, 168 images/run).

fMRI data were analyzed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London). Preprocessing included correction for head motion, spatial normalization, and spatial smoothing with a Gaussian filter (8-mm FWHM). Runs exhibiting a spike of more than 3-mm of scan-to-scan head motion and/or stimulus correlated motion of r >0.5 were dropped. Consequently, eight runs were dropped from each of the control and ADHD groups.

Following preprocessing, statistical analysis was performed at the single-subject level. Each epoch of trials was modeled using a boxcar function convolved with a canonical hemodynamic response function (30). Low-frequency components of the blood-oxygen-level-dependent (BOLD) fMRI signal were modeled as confounding covariates (30). Our contrast of interest was the 2-back minus X-task consistent with previous studies (19,29). All contrast values were saved for use in group analyses and submitted to a second level analysis in which subjects were treated as a random effect. A 2 × 2 ANOVA (using a four-group one-way ANOVA as described in 31) with group and sex as factors was conducted to assess for effects in the BOLD response which was used as a measure of neural activity. (We view fMRI-related findings as reflecting neural activation (32)). Whole brain analyses were conducted to assess for the effects of group (control>ADHD; ADHD>control) and sex (males>females; females>males), and the group-by-sex interaction (control males-ADHD males > control females-ADHD females; and control females-ADHD females > control males-ADHD males). We had an *a priori* hypothesis that, relative to the control group, ADHD adults would have lower levels of activation in the right dorsolateral prefrontal cortex because: 1) this type of n-back task has been shown to be reliant on the dorsolateral prefrontal cortex (29); 2) ADHD theories postulate right frontal cortex abnormalities (20,21); 3) relative to controls, ADHD males have been shown to have less activation in prefrontal regions (8); and 4) we observed a trend in this area previously (19). Therefore, we conducted region-of-interest analyses for the right dorsolateral prefrontal cortex using the same center coordinates (x=33, y=39, z=21) used previously (19) based on Cohen's (29) original n-back study. According to anatomical and MRI studies, our region of interest approximating BAs 46 and 9, extends for approximately 40-mm in both the anterior/posterior and vertical dimensions (33,34). We therefore used a 20-mm radius.

ANCOVAs were conducted to assess confounding effects of depression, tension/anxiety, and age on the interaction effects. For all group analyses, statistical maps were thresholded for cluster-based analyses using a height threshold of p=.005 (uncorrected) and an extent threshold determined by Gaussian random field theory; this conjoint thresholding provides p-values that are corrected for the entire volume (30). Clusters were reported as significant for $p < .05$ (corrected, using Gaussian random field theory (30)). We conducted simple regressions exploring relationships between neural activation and ADHD symptoms.

Results

Demographics

There were no significant differences in the group by sex ANOVAs for age or estimated IQ (Table 1), and ADHD and controls did not significantly differ in sex ratio ($\chi^2(1)=.264$, p>.05). Group by sex ANOVAs for current levels of depression and anxiety showed group effects for POMS depression ($F(1,89)=14.1$, $p < .001$) and tension/anxiety ($F(1,89)=12.6$, $p < .005$) and sex effects for depression ($F(1,89)=13.0$, $p < .005$), but no interactions. ADHD subjects had higher levels of depression and anxiety than controls, and males had higher levels of depression than females.

Behavioral Data Analyses

No significant differences were found in the group by sex ANOVAs on any of the task performance measures (Table 1 in Supplemental Data).

Functional Imaging Analyses

ANOVA analyses for the 2-back minus X-task contrast

Effects of group (ADHD-vs-controls): Whole brain analyses showed that, relative to controls, ADHD adults showed less activation in one left prefrontal cluster. The right prefrontal region of interest analysis showed ADHD adults to have relatively less activation than controls within the right prefrontal region (Table 2; Fig. 1). There were no regions for which ADHD adults showed greater activation than controls.

Effects of sex (males-vs-females): Males had significantly greater activation than females in the right inferior parietal lobule; females showed significantly greater activation than males in the left insula, putamen, and pallidum (Table 2; Fig. 1).

Group-by-sex interaction (control males-ADHD males > control females-ADHD females; and vice versa): A significant group-by-sex interaction indicated that the male 'control-vs-ADHD' difference was larger than the female 'control-vs-ADHD' difference in frontal, temporal, cerebellar, occipital, and subcortical regions (Table 3; Fig. 2).

To determine whether these interaction effects were due to control males showing greater activation than ADHD males, we masked the simple effect of diagnosis in males (control male > ADHD male) with the interaction map (using whole brain and frontal region of interest analyses). These results indicated that for nearly all the regions significant in the interaction including the right frontal and subcortical as well as left cerebellar and occipital regions (Table 3), ADHD males had less activation relative to control males. There were no regions for which the female between group differences in the sex-by-group interaction were greater than the male between group differences, nor were there significant differences between the female groups (See Supplemental Data).

Depression, tension/anxiety, and age ANCOVA analyses revealed that these variables were not accounting for the interaction effects. Comparison of groups with different psychostimulant histories revealed no differences between groups. (See Supplemental Data for details on these and other analyses.)

Exploratory Symptom Correlation Analyses

Correlation analyses between BOLD signal of the 2-back minus X-task contrast with number of *hyperactive* symptoms for ADHD males showed a negative correlation in one cluster encompassing cerebellar and occipital regions (maximum voxel $r = -0.74$; Supplemental Data Table 2, Fig. 1). There were no correlations with *inattentive* symptoms.

In contrast, ADHD females showed a negative correlation between *inattentive* symptoms and neural activation in a cluster spanning numerous cortical and subcortical brain regions (maximum voxel $r = -0.84$; Supplemental Data Table 2, Fig. 1). There were no correlations with *hyperactive* symptoms.

Discussion

We used fMRI and a working memory task to examine sex differences in neural activation in adults with ADHD. Interaction analyses revealed greater differences in neural activation between male (ADHD-vs-control) than between female groups. Whereas ADHD males showed less activation in various brain regions relative to control males, ADHD females showed no significant differences from control females. To our knowledge, this is the first fMRI study to demonstrate significant sex difference interactions in persons with ADHD.

These findings expand working memory findings in ADHD adults, and highlight the importance of obtaining large enough samples to assess sex differences. When male and female subjects were combined, only regions in bilateral prefrontal cortices were significantly different between ADHD adults and controls. However, examination of the sexes separately, revealed that compared to same-sex, matched controls, male and female ADHD adults had different patterns of neural activation for this n-back task. Compared to controls, ADHD males showed relatively less activation in a network of brain regions that was lateralized to right frontal and subcortical regions, and left occipital and cerebellar regions. This pattern of neural activation differences is consistent with hypotheses and other work suggesting right frontal abnormalities in ADHD (19,20), as well as a pre-established hypothesis regarding abnormal cerebellar-prefrontal-striatal networks in ADHD (21), at least in males.

Relative to the control females, ADHD females did not show neuroimaging differences while performing the working memory task. Nonetheless, ADHD females had similar levels of ADHD symptomatology and similar behavioral performance as ADHD males. These findings suggest several possibilities. It could be that the functional neuroanatomical abnormalities associated with certain cognitive functions in ADHD females are not as severe as they are in males, or that the neural network associated with the clinical phenomenology of ADHD is not also associated with performance or brain activation on this working memory task in females. It could also be that normal sexual dimorphisms protect females on this particular task.

These negative findings for adult females with ADHD are largely consistent with the only two functional imaging studies using all female samples in ADHD. In one study, there were no differences between ADHD and control female adolescents in rates of glucose metabolism while performing an attention task (10). In another study (11), there were no differences in degree of functional activation across working memory load between ADHD and control female adolescents. Thus, these data indicate a lack of differences between ADHD and control females in regions shown to have relatively robust differences in studies using mostly or all male subjects (8). Nonetheless, these previous studies of females examined adolescents and thus the studies' effects could be weaker due to subjects being in various developmental stages.

Consistent with other previous findings (11,19,35) there were no significant differences in behavioral task performance between ADHD and controls. The lack of behavioral differences in our study was by design. First, we matched on IQ, which also partially matched on working memory since these two variables are often significantly correlated (36; for this sample $r=.50$, $p<.001$, between IQ and 2-back percent correct). Second, the mean IQs of our ADHD and control groups are above average (118 and 114 respectively), increasing the likelihood that subjects would perform the task well given the significant correlation between working memory and IQ. Finally, as has been recommended (37), we chose a task on which we expected our subjects to perform well, so that we could interpret the neuroimaging findings without the confound of additional error-related activation for the ADHD group. Despite the absence of behavioral differences, we found brain function differences between male, but not female, ADHD and control groups in regions that comprise a network predicted to be abnormal in ADHD, supporting the hypothesis that ADHD affects males and females differently. It is possible that the imaging data are a more sensitive indicator of an alteration in function than are the behavioral data, as our findings are consistent with several other ADHD imaging studies in which functional differences were found despite no significant differences in behavioral performance (19,22,35). It is also possible that neural reorganization and/or different functional connectivity patterns, which may be idiosyncratic or diffuse, could have developed to compensate for the lower

activation observed in the ADHD males relative to their controls. Future research employing parametric versions of this task with more challenging difficulty levels may help to clarify the complex relationship between working memory demand, performance deficits, and neural processing in ADHD adults.

Exploratory analyses demonstrated that neural activity during the working memory task showed negative correlations between brain regions and number of hyperactive symptoms for males and inattentive symptoms for females. Consistent with our findings, previous studies that included mostly or all male subjects found negative correlations between the BOLD signal and hyperactive symptoms, and no correlations with inattentive symptoms (if examined;6,22). Overall, this suggests a negative relationship between task-related neural activity and severity of ADHD which may differ by sex and symptom subtype. Understanding more about these correlations could lend insight into why females are more likely than males to have the inattentive subtype of ADHD (12).

Our findings need to be considered in light of methodological limitations. Although no participants in this study were taking psychotropic medications at the time of scan and the number of stimulant naïve subjects was approximately equal across sexes, there were variable histories of past psychotropic medication usage. However, imaging data analyses between groups with different psychostimulant histories (i.e., past, never or current use) revealed no differences. Also, a portion of our subjects no longer met the DSM-IV symptom threshold criterion at the time of the interview. These subjects were fairly evenly distributed across sexes and a subthresthold number of symptoms is common in adult ADHD (38). If anything, we would predict that inclusion of subthreshold subjects may have resulted in weaker study effects rather than creating spurious significant effects. Furthermore, the diagnoses of adult ADHD relied on self-report using an interview derived from the Kiddie-SADS-E. Nonetheless, we are confident in our diagnoses as there is substantial evidence for the validity of diagnoses made in this manner (26). Additionally, there were variable rates of lifetime comorbidities for depression and anxiety. Using current POMS levels of depression and anxiety as covariates in the analyses had no significant effect on our results indicating that these variables were not accounting for the observed differences. Even so, we used the POMS, and other popular scales such as the Hamilton could have been used which would have assessed mood differently. Also, given our samples' higher than average mean IQs, it is unclear how these results may generalize to ADHD adults with average mean IQs. Yet, a substantial portion of our subjects' had "normal" IQs. Future work should examine the effects of IQ on neural functioning. Finally, we reiterate that we interpreted changes in the BOLD response as neural activation. Also, spatial resolution was limited by the 8-mm FWHM smoothing filter.

In sum, relative to controls, we found less neural activity in cortical, subcortical and cerebellar regions for male but not female ADHD adults during performance on a working memory task. These data suggest that it is important to take sex into account when studying the functional neuroanatomy of ADHD, as failure to do so may mask important neural differences observed solely in males or females. These findings also indicate that neuroimaging findings from studies using mostly or all males, which account for most studies, may not necessarily apply to females. Thus, these results may be important with regards to treatment issues for females. Follow-up studies using frontal, cerebellar and striatal regions-of-interest could be fruitful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Faraone SV. The scientific foundation for understanding attention-deficit/hyperactivity disorder as a valid psychiatric disorder. Eur Child Adolesc Psychiatry. 2005; 14:1–10. [PubMed: 15756510]
2. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006; 163:716–723. [PubMed: 16585449]
3. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry. 2005; 57:1215–1220. [PubMed: 15949990]
4. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007; 61:1361–1369. [PubMed: 16950217]
5. Durston S, Mulder M, Casey BJ, Ziermans T, van Engeland H. Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. Biol Psychiatry. 2006; 60:1062–1070. [PubMed: 16712804]
6. Rubia K, Smith AB, Brammer MJ, Toone B, Taylor E. Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry. 2005; 162:1067–1075. [PubMed: 15930054]
7. Pliszka SR, Glahn DC, Semrud-Clikeman M, Franklin C, Perez R 3rd, Xiong J, Liotti M. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. Am J Psychiatry. 2006; 163:1052–1060. [PubMed: 16741206]
8. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry. 2006; 47:1051–1062. [PubMed: 17073984]
9. Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, Vaituzis AC, Blumenthal JD, Nelson J, Bastain TM, Zijdenbos A, Evans AC, Rapoport JL. Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2001; 58:289–295. [PubMed: 11231836]
10. Ernst M, Cohen R, Liebenauer L, Jons P, Zametkin A. Cerebral glucose metabolism in adolescent girls with attention-deficit/hyperactivity disorder. J Am Acad Child Adoles Psychiatry. 1997; 36:1399–1406.
11. Sheridan MA, Hinshaw S, D'Esposito M. Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007; 46:1357–1366. [PubMed: 17885578]

12. Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, Wilens TE, Frazier E, Johnson MA. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry. 2002; 159:36–42. [PubMed: 11772687]
13. Andreason PJ, Zametkin AJ, Guo AC, Baldwin P, Cohen RM. Gender-related differences in regional cerebral glucose metabolism in normal volunteers. Psychiatry Res. 1994; 1:175–83. [PubMed: 8022952]
14. Ragland JD, Coleman AR, Gur RC, David C, Glahn DC, Gur RE. Sex differences in brain-behavior relationships between verbal episodic memory and resting regional cerebral blood flow. Neuropsychologia. 2000; 38:451–461. [PubMed: 10683395]
15. Holden C. Sex and the suffering brain. Science. 2005; 308:1574. [PubMed: 15947170]
16. Faraone SV, Biederman J, Spencer T, Wilens T, Seidman LJ, Mick E, Doyle A. Attention deficit hyperactivity disorder in adults: an overview. Biol Psychiatry. 2000; 48:9–20. [PubMed: 10913503]
17. Biederman J, Faraone SV, Monuteaux MC, Bober M, Cadogen E. Gender effects on attention-deficit/hyperactivity disorder in adults, revisited. Biol Psychiatry. 2004; 55:692–700. [PubMed: 15038997]
18. Ernst M, Liebenauer LL, King AC, Fitzgerald GA, Cohen RM, Zametkin AJ. Reduced brain metabolism in hyperactive girls. J Am Acad Child Adoles Psychiatry. 1994; 33:858–868.
19. Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:439–447. [PubMed: 15737657]
20. Clark L, Blackwell AD, Aron AR, Turner DC, Dowson J, Robbins TW, Sahakian BJ. Association between response inhibition and working memory in adult ADHD: a link to right frontal cortex pathology? Biol Psychiatry. 2007; 61:1395–1401. [PubMed: 17046725]
21. Giedd JN, Blumenthal J, Molloy E, Castellanos FX. Brain imaging of attention deficit/hyperactivity disorder. Ann N Y Acad Sci. 2001; 931:33–49. [PubMed: 11462751]
22. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007; 61:720–724. [PubMed: 16950228]
23. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders. Washington, D.C: American Psychiatric Press; 1997.
24. Orvaschel, H.; Puig-Antich, J. Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiologic Version. Fort Lauderdale, FL: Nova University; 1987.
25. Biederman J, Faraone SV, Knee D, Munir K. Retrospective assessment of DSM-III attention deficit disorder in non-referred individuals. J Clin Psychiatry. 1990; 51:102–106. [PubMed: 2307663]
26. Faraone SV, Biederman J, Feighner JA, Monuteaux MC. Assessing symptoms of attention deficit hyperactivity disorder in children and adults: Which is more valid? J Consult Clin Psychol. 2000; 68:830–842. [PubMed: 11068969]
27. McNair, DM.; Lorr, M.; Droppleman, LF. EdITS Manual for the Profile of Mood States (POMS). San Diego, CA: EdITS/Education and Industrial Testing Service; 1992.
28. Wechsler, D. Wechsler Adult Intelligence Scale III [manual]. 3. San Antonio, TX: The Psychological Corporation; 1997.
29. Cohen JD, Forman SD, Braver TS, Casey BJ, Serven-Schrelber D, Noll DC. Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Hum Brain Mapp. 1994; 1:293–304.
30. Friston, KJ.; Ashburner, JT.; Kiebel, SJ.; Nichols, TE.; Penny, WD., editors. Statistical Parametric Mapping: The Analysis of Functional Brain Images. London: Academic Press; 2007.
31. Henson, RNA.; Penny, WD. Technical Report. 2003. ANOVAs and SPM: Wellcome Department of Imaging Neuroscience.
32. Buxton, RB., editor. Introduction to Functional Magnetic Resonance Imaging Principles and Techniques. Cambridge: University Press; 2002.
33. Talairach, J.; Tournoux, P. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers, Inc; New York: 1988.

34. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic Definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. Cerebral Cortex. 1995; 5:323–337. [PubMed: 7580125]

35. Mostofsky SH, Rimrodt SL, Schafer JG, Boyce A, Goldberg MC, Pekar JJ, Denckla MB. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. Biol Psychiatry. 2006; 59:48–56. [PubMed: 16139806]

36. Colom R, Rebollo I, Palacios A, Juan-Espinosa M, Kyllonen P. Working memory is (almost) perfectly predicted by “g”. Intelligence. 2004; 32:277–296.

37. Price CJ, Friston KJ. Scanning patients with tasks they can perform. Hum Brain Mapp. 1999; 8:102–108. [PubMed: 10524600]

38. Faraone SV, Biederman J, Spencer T, Mick E, Murray K, Petty C, Adamson JJ, Monuteaux MC. Diagnosing adult attention deficit hyperactivity disorder: Are late onset and subthreshold diagnoses valid? Am J Psychiatry. 2006; 163:1720–1729. [PubMed: 17012682]

39. Weissman MM, Leckman JF, Merikangas KR, Gammon GD, Prusoff BA. Depression and anxiety disorders in parents and children. Results from the Yale family study. Arch Gen Psychiatry. 1984; 41:845–852. [PubMed: 6466043]

40. Mennin DS, Biederman J, Mick E, Faraone SV. Towards defining a meaningful anxiety phenotype for research in ADHD children. J Atten Disord. 2000; 3:192–199.

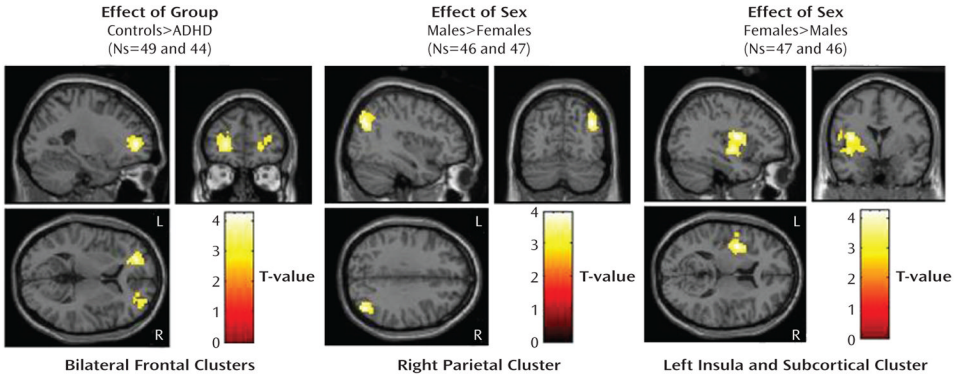

Figure 1.

Results of the 2 × 2 ANOVA showing effects of group and sex. Images depict significant differences in working memory related activation (2-back minus X-task contrast) for the groups presented. There were no regions for which ADHD adults showed greater activation than control subjects. Left side is left hemisphere in the coronal view. Clusters are significant at $p < .05$ (corrected). ADHD, attention-deficit/hyperactivity disorder. R = right; L = left.

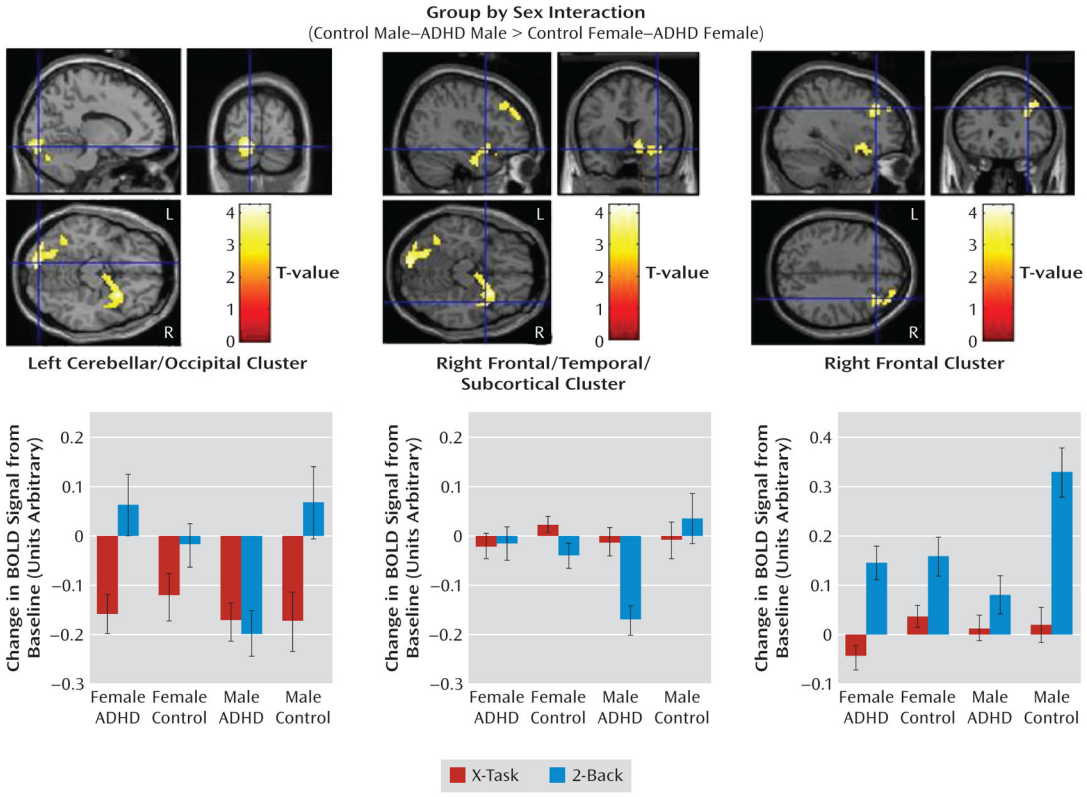

Figure 2.

Top panel: Results of the 2 × 2 ANOVA showing the significant group by sex interaction. Images depict regions for which the male (control - ADHD) difference for the working memory related activation (2-back minus X-task contrast) is significantly greater than the female (control - ADHD) difference. The *right* subcortical/prefrontal and *left* cerebellar/occipital pattern of differences can be seen in the axial images. Crosshairs indicate the location of the clusters labeled beneath each image. There were no regions for which the differences between female groups were larger than for the male groups. Ns = 23, 23, 26, and 21 for the control male, ADHD male, control female, and ADHD female groups respectively. Left side is left hemisphere in the coronal view. Clusters are significant at $p < .05$ (corrected). ADHD, attention-deficit/hyperactivity disorder. R = right; L = left.

Bottom panel: Graphs of average BOLD signal change from baseline. Each bar represents the beta value for all voxels averaged within each cluster for the X-task and 2-back task for each group separately by sex. As can be seen from the graphs of the beta values, the primary differences between groups are in levels of activation for the ADHD males while performing the 2-back task. Across all three regions, the ADHD males are always consistently activating less or *de*activating more than any of the other three groups. Also, all four groups show a relatively similar pattern of activation for the X-task. The groups do not differ much, if at all, from zero for either the frontal or the frontal/subcortical cluster. However, all four groups show deactivations for the X-task for the occipital/cerebellar cluster. There were no significant group by sex interactions for the X-task.

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Table 1

Demographics and behavioral data

	All Subjects				Females				Males			
	ADHD (N=44)		Controls (N=49)		ADHD (N=21)		Controls (N=26)		ADHD (N=23)		Controls (N=23)	
Age (years)	36.8	(11.0)	32.5	(10.1)	37.1	(12.5)	32.7	(10.8)	36.6	(9.8)	32.3	(9.5)
Age Range (years)	19–54		18–53		19–54		18–53		20–53		19–51	
Estimated IQ[a]	118.1	(14.3)	114.0	(12.6)	116.0	(11.6)	111.2	(12.2)	120.2	(16.4)	117.1	(12.7)
Age of ADHD Onset	5.0	(2.5)	----	----	5.1	(3.1)	----	----	4.8	(1.8)	----	----
Number of Hyperactive-Impulsive Symptoms	4.2	(2.5)	----	----	4.5	(2.4)	----	----	3.9	(2.6)	----	----
Number of Inattentive Symptoms	5.9	(2.0)	----	----	5.6	(1.9)	----	----	6.1	(2.2)	----	----
POMS - Depression[b]	39.8	(5.1)	36.5	(3.4)	38.0	(4.8)	35.2	(2.6)	41.4	(4.9)	37.9	(3.6)
POMS - Tension/Anxiety[c]	36.5	(6.8)	32.0	(5.2)	35.7	(6.8)	30.5	(3.4)	37.2	(6.9)	33.6	(6.4)
Depression[d] (lifetime)[e]	6	14%	3	6%	4	19%	1	4%	2	9%	2	8%
≥ 2 Anxiety disorders[f] (lifetime)[e]	12	27%	2	4%	10	48%	2	8%	2	9%	0	0%

Data presented as Mean (SD) unless otherwise indicated. Unless otherwise noted, ANOVA $p > .05$. ADHD = attention-deficit/hyperactivity disorder; POMS = Profile of Mood States.

[a] Estimated IQ is obtained from the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale – III. IQ data for 1 female control and 1 ADHD male were lost.

[b] Group by sex ANOVA indicated that ADHD subjects had higher levels of depression than controls, and males had higher levels of depression than females.

[c] Group by sex ANOVA indicated that ADHD subjects had higher levels of anxiety than controls.

[d] As suggested by others (39), the diagnosis of major depression was made only if the depressive episode was associated with marked impairment. Data presented as N and %.

[e] There were no subjects in any of the four groups who met criteria for depression or anxiety at the time of the clinical interview.

[f] Since there are many anxiety disorders measured by our structured interviews, we aggregated them into a binary measure coded positive if two or more anxiety disorders were endorsed, and negative otherwise. We previously found this summary variable to measure a meaningful anxiety syndrome (40). Data presented as N and %.

Table 2

Results of ANOVA effects of group and sex showing brain regions for which groups differed for working memory related activation (2-back minus X-task contrast)

			MNI Coordinates		
Comparison and significant regions	**K (Cluster Extent)**	**Peak *t***	**x**	**y**	**z**
Effect of group					
Controls > ADHD					
L middle frontal gyrus (BA 9) (extends to L frontal pole (BA 9/10) and paracingulate (BA 32))	213	4.28	−24	48	6
R middle frontal gyrus (BA 10)	56	3.25	33	57	15
ADHD > Controls					
No significant differences	---	---	---	---	---
Effect of sex					
Males > Females					
R inferior parietal lobule (angular gyrus (BA 39))	176	3.94	39	−72	33
Females > Males					
L insula (extends to L putamen and pallidum)	425	4.28	−36	0	12

Clusters are significant at $p < .05$ (corrected). There were no regions for which the ADHD adults showed greater activation than the control adults for any of the comparisons. For ADHD and controls Ns = 44 and 49 respectively; for males and females Ns = 46 and 47 respectively; for control males. ADHD = attention-deficit/hyperactivity disorder; R = right; L = left.

Table 3

Results of ANOVA effects of the group by sex interaction showing brain regions for which groups differed for working memory related activation (2-back minus X-task contrast)

Comparison and significant regions	K (Cluster Extent)	Peak *t*	MNI Coordinates x	y	z
Group by sex interaction (Control males - ADHD males > Control females - ADHD females)					
L temporo-occipital cortex (fusiform cortex (BA 37/19)) (extends to L lingual gyrus (BA 19/18/17), cerebellar hemisphere)	352	4.29	−12	−90	−12
R orbitofrontal cortex (BA 47/12) (extends to R basal forebrain, inferior frontal gyrus (pars orbitalis (BA 47)), insula, superior, middle & inferior temporal gyri (BA 22, 21, 20), nucleus accumbens, hypothalamus, pallidum, putamen)	239	4.25	27	12	−15
R middle frontal gyrus (BA 8/9/10)	174	3.66	33	30	36
Simple effect of group for males masked by significant interaction					
R pallidum (extends to R basal forebrain, orbitofrontal cortex (BA 47/12), inferior frontal gyrus (pars orbitalis (BA 47)), putamen, insula, nucleus accumbens, hypothalamus)	199	4.89	12	3	−9
L temporo-occipital cortex (fusiform cortex (BA 37/19)) (extends to L lingual gyrus (BA 19/18/17), cerebellar hemisphere)	287	4.50	−39	−54	−12
R middle frontal gyrus (BA 8/9)	48	3.99	33	27	33
Group by sex interaction (Control females - ADHD females > Control males - ADHD males)					
No significant differences	---	---	---	---	---

Clusters are significant at $p < .05$ (corrected). There were no regions for which the ADHD adults showed greater activation than the control adults for any of the comparisons. For control males, ADHD males, control females and ADHD females Ns = 23, 23, 26 and 21 respectively. ADHD = attention-deficit/hyperactivity disorder; R = right; L = left.

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