Differential brain activation during response inhibition in bipolar and attention-deficit hyperactivity disorders

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Abstract

Aim: To identify differential patterns of brain activation between adolescents with bipolar disorder and adolescents with attention-deficit hyperactivity disorder (ADHD) to better understand the neurophysiology of both disorders. We hypothesized that subjects with ADHD would show altered activation in brain regions involved in executive and sustained attention. In contrast, we hypothesized that bipolar subjects would show altered brain activation in regions responsible for emotionally homeostasis, including the striatum and amygdala.

Methods: Functional magnetic resonance imaging was performed during a continuous performance task with a response inhibition component in 11 adolescents with bipolar disorder during a manic episode, 10 adolescents with ADHD, and 13 healthy adolescents.

Results: There were no differences in behavioural performance among the three groups. Compared with bipolar subjects, subjects with ADHD showed increased activation in the superior temporal lobe during successful response inhibition. Although bipolar subjects did not show activation differences in the striatum or amygdala compared with ADHD subjects, increased left parahippocampal activation in the bipolar group was associated with increased manic symptoms.

Conclusions: The patterns of brain activation observed in the current study support divergent patterns of neurophysiological dysfunction in individuals with bipolar disorder as compared with those with ADHD. Therefore, the impulsive behaviour seen in both disorders may be the consequence of dysfunction in different brain regions, and further research may help identify neurobiological markers that are specific to each condition.

Keywords

attention; attention-deficit hyperactivity disorder; bipolar disorder; fMRI; neurophysiology

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INTRODUCTION

Despite the high co-occurrence of adolescent bipolar and attention-deficit hyperactivity disorders (ADHD), the relationships between these conditions remain unclear.[1] Adolescents with bipolar disorder are often initially misdiagnosed with ADHD and treated with medications that may exacerbate their mood symptoms.[2] Impulsivity and inattention are two underlying features associated with bipolar disorder and ADHD.[3–6] Mayberg and colleagues suggest that in the presence of a mood disorder, attentional disturbances may represent a marker of dysfunction in brain regions that are primarily involved in mood regulation.[7] In contrast, in primary disorders of attention such as ADHD, neuronal dysfunction may primarily involve brain regions associated with attention.[8] Given the reciprocal connections between emotional and cognitive brain systems, impaired cognition could then lead to dysregulation of mood. Comparing brain networks associated with inattention and impulse control in adolescents with bipolar disorder versus adolescents with ADHD may help to identify neurobiological markers that are specific to each condition.

Prior research has shown that bipolar patients in a manic episode and patients with ADHD have significant difficulty with inhibitory control.[9–11] The majority of functional magnetic resonance imaging (fMRI) studies of ADHD and several studies of bipolar disorder have used response inhibition tasks to examine brain regions involved in attention and impulsivity.[8,12–15] However, a significant limitation of these studies is that none of them directly compared subjects with ADHD with those with bipolar disorder; rather, they compared each group to healthy subjects. In a more direct comparison of bipolar and ADHD patients, Adler *et al.*[16] examined neurophysiological differences between these groups by comparing bipolar adolescents with and without co-morbid ADHD during a manic episode. The authors were interested in brain activation differences in the two groups during sustained attention and therefore examined subjects with fMRI during a continuous performance task (CPT). Bipolar subjects with co-morbid ADHD showed greater brain activation in posterior brain regions, including the temporal cortex during the task.[16] Strakowski *et al.*[17] then added a stop signal component to this CPT task to measure response inhibition. This modified CPT task allows for the measure of response inhibition within a background of sustained attention and was proposed as a more challenging and ecologically valid measure of response inhibition.

To test the hypothesis that different brain regions contribute to the deficits in response inhibition seen in ADHD and bipolar disorder, we studied adolescent subjects with each disorder along with healthy subjects while subjects performed the modified CPT task during fMRI. Based on prior neuroimaging work in ADHD,[15,18] we hypothesized that compared with bipolar and healthy subjects, ADHD subjects would show altered activation in the anterior cingulate and dorsal prefrontal regions involved in executive attention. Based on the findings by Adler *et al.*[16], we also hypothesized that subjects with ADHD would show increased activation in the temporal cortex compared with bipolar subjects. In bipolar patients, because attentional deficits may represent problems with emotional regions of the brain, we hypothesized that compared with ADHD and healthy subjects, bipolar patients would exhibit altered activation in regions responsible for emotional homeostasis.[19] Specifically, we predicted bipolar subjects would show increased activation in the amygdala

and striatum. Prior studies in adolescents with bipolar disorder have consistently found altered activation in these two regions.[20–24]

METHODS

Subjects

Adolescents with bipolar disorder ($n = 14$) and adolescents with ADHD ($n = 14$) were recruited from the Cincinnati Children's Hospital Medical Centre. Subjects with bipolar disorder were included if they met DSM-IV criteria for bipolar I disorder, current episode manic or mixed, did not have a history of co-occurring ADHD and had a Young Mania Rating Scale (YMRS)[25] score 20. Subjects with ADHD were recruited if they met DSM-IV criteria for ADHD and had no history of a mood or psychotic disorder themselves or in any first-degree relative. Overall, there was very little co-morbidity in either patient group. In the bipolar group, four subjects had co-morbid diagnoses: one subject with alcohol dependence, one subject with simple phobia, one subject with conduct disorder and one subject with generalized anxiety disorder. In the ADHD group, only four patients had co-morbid diagnoses: two subjects with transient tic disorder and two subjects with oppositional defiant disorder.

Demographically matched healthy adolescents ($n = 14$) were also recruited. Healthy subjects had no history of Axis I psychiatric disorders themselves or in any first-degree relative. All subjects were between the ages of 11 and 18 years, were physically and neurologically healthy, and if female, had a negative urine pregnancy test. Other exclusion criteria were any lifetime substance dependence or illicit substance use within the last 3 months, medical or neurological illnesses that might influence brain structure or function, contraindications to receiving an MRI, and diagnosis of mental retar-dation or a documented IQ below 70 using the Wechsler Abbreviated Scale of Intelligence.

Bipolar, ADHD and healthy subjects were not taking medications at the time of the fMRI scan. Eight of the ADHD subjects were taking stimulants, which were held the morning of the scan. All bipolar subjects had been off atypical anti-psychotics for at least 72 h and had undetectable levels of mood stabilizers. All medications were self-discontinued, and no medications were stopped for the study. Healthy subjects were not taking medications. Adolescents provided written assent, and their legal guardians provided written informed consent for study participation after study procedures were fully explained. The study was approved by the Investigational Review Boards of the University of Cincinnati and the Cincinnati Children's Hospital Medical Centre and conformed to the provisions of the Declaration of Helsinki. Diagnoses were made using the Washington University at St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia[26] by trained child and adolescent psychiatrists with established diagnostic reliability (kappa = 0.94).[2] Depressive and manic symptoms were evaluated using the Children's Depression Rating Scale-Revised Version (CDRS) and YMRS, respectively.[25,27] The interrater reliability for total scores on the CDRS and YMRS was measured with the interclass correlation coefficient (ICC) and was judged to be good (ICC > 0.80).[28]

CPT-X task

During the MRI scan, all subjects performed a CPT-X task. This task builds on a CPT task that is purposefully undemanding and incorporates a stop signal component (Strakowski go-no-go 2008 and Birkett *et al.*). Sustained attention is engaged by having subjects press on the target, a blue X presented in the centre of the visual field. Blue Xs were randomly interspersed with other blue letters that were not targets. The response inhibition component was added by including a 'stop' signal, a red X that replaced the blue X after variable time intervals (0, 50, 100 or 150 ms). A measure of inhibitory control is then provided by the percentage of correct stops.

All stimuli were presented for 450 ms, with an inter-trial interval of 50 ms. Responses were counted as part of the trial if they were recorded within 800 ms of the stimulus onset. Subjects were instructed to press a button as quickly and accurately as possible every time a blue X occurred, but to resist responding if the colour of the target changed to red. A total of 1919 trials in a 16-min fMRI scanning run were presented, including 197 'go' trials (blue X), 64 'stop' trials (red X) and 1658 non-targets. The task was written and displayed using PsyScope software[29] (http://psy.ck.sissa.it/). Responses were recorded using a MRI-compatible button box. One subject with ADHD could not be used in the analysis because behavioural data were not recorded in the scanner due to a hardware malfunction. Two subjects with bipolar disorder were not further analysed because they did not correctly respond to greater than 10% of the blue X trials.

Imaging

All subjects were scanned at the University of Cincinnati College of Medicine's Centre for Imaging Research using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system (Varian Inc., Palo Alto, CA, USA). Following a three-plane gradient echo scan for alignment and brain localization, a shim procedure was performed to generate a homogeneous magnetic field. To provide anatomical localization for activation maps, a high-resolution, T1-weighted, 3-D brain scan was obtained using a modified driven equilibrium Fourier transform (MDEFT) sequence (T_{MD} = 1.1 s, time to repetition (TR) = 13 ms, echo time (TE) = 6 ms, field of view (FOV) = 25.6 × 19.2 × 19.2 cm, matrix 256 × 192 × 96 pixels, flip angle = 20 degrees). A mid-sagittal localizer scan was obtained to place 30 contiguous 5-mm axial slices extending from the inferior cerebellum to encompass the entire brain. Subjects then completed an fMRI session in which scans were acquired while performing the response inhibition task using a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence (TR/TE = 2000/30 ms, FOV = 25.6 × 25.6 cm, matrix 64 × 64 pixels, slice-thickness=5 mm, flip angle = 75 degrees).

fMRI analysis

The fMRI data were analysed using AFNI (Analysis of Functional NeuroImages; http://afni.nimh.nih.gov/afni).[30] Following acquisition, the MRI images were reconstructed using in-house software developed in IDL (interactive data language), which converts raw scanner data into AFNI format. In AFNI, MDEFT (structural) and EPI (functional) images were co-registered using scanner coordinates. Average motion was calculated for each subject, and all subjects had less than 4 mm of uncorrected movement across the run before motion

correction. There were no differences in average uncorrected motion among the three groups (F = 1.175, P = 0.32). Functional images were corrected for motion using a six-parameter rigid body transformation.[31] In addition, each volume was inspected for signal artefact using a semi-automated algorithm in AFNI to identify questionable TRs. These volumes were removed from further analysis if visual inspection indicated uncorrectable head movement, that is within-TR head motion, or greater than 30% of voxels were greater than 2 standard deviations from the mean signal intensity. On average, we removed 10 volumes (4%) from each person, and two ADHD and one healthy subject were excluded from further analysis because greater than 40% of the TRs were removed.

Using tools in AFNI, anatomical and functional maps were transformed into stereotaxic Talairach space using the ICBM452 template and spatially blurred to twice the voxel dimensions. Binary masking was applied to each image to remove pixels outside the brain. Individual activation maps were then created for each subject using a deconvolution algorithm that compares the actual hemodynamic response to a canonical hemodynamic response function (a gamma function), creating voxel-wise t-maps. Event-related hemodynamic response functions were calculated for correct delayed STOPs (red X) and correct non-responses to distracter stimuli (non-X). General linear tests were then performed on each subject to determine contrasts of correct delayed red X's versus correct non-responses to non-X's. Individual activation maps were then averaged across subjects, and the final regression analysis was performed to contrast the three groups with 11 bipolar, 10 ADHD and 13 healthy subjects. Two bipolar and one ADHD subject were lost because of poor (less than 15% correct on Blue-X trials) or missing behavioural data, and one bipolar, two ADHD and one healthy subject were excluded because of within-TR head motion. Group activation maps were corrected to P 0.05 using a threshold probability of P 0.05 and a voxel-level correction of 137 contiguous voxels, as determined by Monte Carlo simulations within AFNI.[32,33]

RESULTS

There were no statistically significant group differences in age, sex, race or IQ among the three groups (see Table 1). There were statistically significant group differences in YMRS and CDRS scores, essentially by definition (see Table 1). *Post-hoc* tests (Tukey's honestly significant differences) were performed and indicated that bipolar subjects had significantly higher YMRS scores than ADHD (P 0.001) and healthy subjects (P 0.001), and ADHD subjects had significantly higher YMRS scores than healthy subjects (P 0.002). Bipolar subjects had significantly higher CDRS scores than ADHD (P 0.001) and healthy (P 0.001) subjects, but there were no statistically significant difference in CDRS scores between ADHD and healthy subjects (P = 0.347).

Regarding behavioural performance, there were no statistically significant differences in reaction time or percent accuracy of correct blue-X trials or delayed red-X trials among the three groups (see Table 2). In addition to total performance, percent accuracy scores were also calculated for each half of the scan to determine if performance varied during the 16 minutes task. Repeated measures ANOVAs were performed, and there was a main effect of trial time for blue-X (F = 37, P 0.001) and red-X (F = 15, P 0.001) trials. All subjects

had significantly lesser accuracy on blue-X trials and significantly greater accuracy on delayed red-X trials during the final 8 minutes. There were no between group differences over time. Finally, to further assess performance, discriminability and bias were calculated. There were no significant differences in either measure (see Table 2).

Significant differences in brain activation occurred during successful response inhibition as measured by the contrast of correct red X (STOP) trials versus correct non-responses to distracter stimuli (non-X) (see Table 3 and Fig. 1). Compared with bipolar subjects, ADHD subjects showed increased activation in the left superior temporal gyrus, right posterior cingulate gyrus, right lingual gyrus, right cuneus, left middle temporal gyrus, right cerebellar tonsil and left insula. See Table 3 for regions that were significant between each patient group and the healthy comparison subjects.

Although gender distribution was not significantly different among the groups, gender was further controlled for by inclusion as a covariate in the group analysis. None of the activation differences in Table 2 overlapped with brain regions associated with gender. Additional analyses were also performed in the bipolar subjects to determine if any of the brain regions activated during successful inhibition in bipolar subjects were correlated with mood state. YMRS and CDRS scores were used as covariates in a regression analysis performed in AFNI. Increased YMRS scores were associated with increased activation in the left parahippocampal gyrus, the right superior temporal gyrus (BA 22) and the right cerebellar tonsil. Increased CDRS scores were associated with decreased activation in the bilateral thalamus, right superior temporal lobe (BA 22) and right posterior cingulate gyrus.

DISCUSSION

To our knowledge, this is the first fMRI study to directly compare adolescents with ADHD with those with bipolar disorder. Adolescents with ADHD and bipolar disorder show unique alterations in brain activation during successful response inhibition despite a lack of differences in behavioural performance on this task. Consistent with our initial hypothesis, subjects with ADHD exhibited increased activation in the superior temporal lobe as compared with subjects with bipolar disorder and healthy subjects, and decreased anterior cingulate activation compared with healthy subjects. Contrary to our hypothesis, there were no differences in striatum or amygdala between the patient groups.

There was a sustained attention decrement over time as expected for CPT performance.[34,35] There was also a high rate of successful 'stops', suggesting that each group inhibited motor responses after the stop signal as appropriate. All three groups showed relatively poor response rates to targets (blue-Xs), suggesting that they adopted a conservative strategy of withholding responses to achieve a high level of stop-signal performance. Group similarities on the signal detection measure of discriminability and bias further confirm that subjects in all three groups were using a similar conservative strategy, that is, delaying their responses to avoid incorrect response on the delayed red-X trials. Another possibility is that the subjects may have inconsistently attended to the task, leading to a low rate of successful target presses and a correspondingly high rate of apparent successful inhibition to the delayed red-X trials. In addition, there may have been some difficulty in clearly

distinguishing the letters and colours inside the scanner. However, the fact that response times were longer than the presentation interval supports the first possibility. In addition, our previous research using a CPT task showed that bipolar and healthy subjects were able to consistently attend to the task.[34,35] To further distinguish between these possibilities, behavioural performances were compared between the first and second half of the task. All three groups had significantly lower accuracy on blue-X trials (i.e. a sustained attention deficit) and significantly greater accuracy on delayed red-X trials the final 8 min. This suggests a practice effect, with subjects using a more conservative strategy as the task progressed and provides evidence that subjects were paying attention throughout the entire task.

The fMRI findings in subjects with ADHD were consistent with previous studies.

Altered activation in the anterior cingulate cortex (ACC) is a common finding in ADHD. The majority of prior studies (9 out of 13) showed decreased ACC activation compared with controls, consistent with the present findings.[15] Increased brain activation in the superior temporal lobe (BA 39), a region important for the alerting and orienting components of attention,[36,37] was also found in ADHD subjects. Altered activation in the superior temporal lobe is a common finding in ADHD, although most often, this region shows decreased activation compared with healthy subjects.[15] However, these studies used a variety of tasks. When prior studies using response inhibition tasks are examined, ADHD subjects consistently show increased activation in the superior temporal lobe compared with healthy subjects.[8,13,14] Subjects with bipolar disorder also showed increased activation in the superior temporal lobe (BA 39) compared with healthy subjects, but in the opposite hemisphere. Given the equal performance in all groups, increased temporal activation may have been needed in both patient groups to compensate for deficits in sustained attention during the CPT portion of the task. It is also possible that increased temporal activation leads to attentional problems. These possibilities could not be differentiated in the current study.

Although bipolar subjects did not show activation differences in the striatum or amygdala compared with ADHD subjects, increased left parahippocampal activation in the bipolar group was associated with increased YMRS scores. The amygdala/hippocampal complex has been hypothesized to regulate emotional homeostasis.[19,38] Activation within the amygdala may increase with worsening mood symptoms and contribute to cognitive symptoms via reciprocal connections to the prefrontal regions. Further studies with larger number of subjects are needed to determine whether amygdala differences exist between the two patient groups.

Several limitations of this study should be considered when interpreting the results. First, the study is limited by the small sample and may not have had sufficient power to detect differences that might be present. Further studies with larger sample sizes are therefore needed. Second, it may be useful to use a more challenging cognitive task to be able to differentiate the patient groups from healthy subjects, although these creates a further confound of performance differences. Third, in the current study, all bipolar patients were manic so that the findings in subjects with bipolar disorder may reflect mood state effects related to mania rather than bipolar disorder per se. Further studies of subjects with bipolar

disorder during depression and euthymia are needed to determine if these brain activation patterns are simply effects of mania. Another potential limitation was the poor performance on the task. This lowered the power of the study, and if this poor performance was related to lack of attention on the task, it may have also biased the neuroimaging results. Finally, while none of the subjects with ADHD were on medications at the time of the scan, eight of the subjects were taking stimulants daily. Although these medications were held the morning of the scan, 24 h off stimulants may not have been long enough to remove the acute effects of these medications on brain activation. Nevertheless, the current study is unique in comparing adolescent subjects with ADHD and bipolar disorder off medication and scanning both groups during a cognitive task. The results indicate there are unique alterations in brain activation patterns in the two patient groups. Therefore, the impulsive behaviour seen in both disorders may be the consequence of dysfunction in different brain regions.

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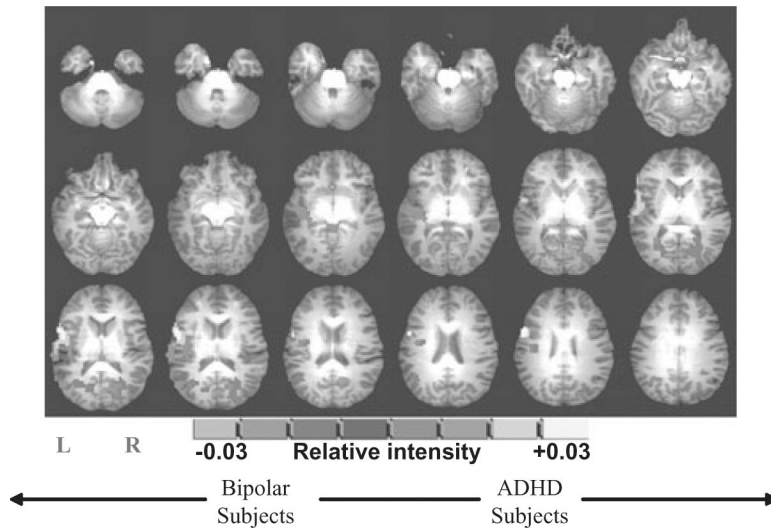Author Manuscript

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FIGURE 1.

Functional activation map showing relative brain activation during response inhibition between patients with attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (all regions were significant at P 0.05). Orange areas represent significantly greater brain activation in ADHD subjects.

TABLE 1.

Demographic measures in patients with BPD, ADHD and healthy comparison subjects

	BPD (N = 11)		ADHD (N = 10)		Healthy subjects (N = 13)			
Gender, N (%) female	7 (64)		3 (30)		6 (46)			
Ethnicity, N (%), white	9 (82)		9 (90)		11 (85)			

	Mean	SD	Mean	SD	Mean	SD	F	P
Age (years)	14.2	1.5	14.0	2.0	14.5	1.9	0.27	0.77
Education (years)	8.1	104	7.8	2.0	8.5	2.0	0.47	0.63
IQ (WASI)[†]	105	8.2	104	15.2	112	14.0	1.29	0.29
YMRS[‡]	26	6.3	8.6	7.5	0.2	0.6	67	0.00
CDRS[§]	43	12.2	22.2	3.5	18	2.3	41	0.00

[†]Three of the bipolar subjects were lost to follow up and did not receive IQ measures.

[‡]*Post hoc* Tukey's HSD tests showed significant differences between bipolar and ADHD subjects (P 0.001), between bipolar and healthy subjects (P 0.001), and between ADHD and healthy subjects (P 0.002).

[§]*Post hoc* Tukey's HSD tests showed significant differences between bipolar and ADHD subjects (P 0.001), and between bipolar and healthy subjects (P 0.001).

ADHD, attention-deficit hyperactivity disorder; BPD, bipolar disorder; CDRS, Children's Depression Rating Scale-Revised Version; HSD, honestly significant differences; SD, standard deviation; WAIS, Wechsler Abbreviated Scale of Intelligence; YMRS, Young Mania Rating Scale.

TABLE 2.

Behavioural performance measures in patients with BPD, ADHD and healthy comparison subjects

Behavioural measure	BPD (N = 11)		ADHD (N = 10)		Healthy subjects (N =13)		F	P
	Mean	SD	Mean	SD	Mean	SD		
Total accuracy blue X (%)	42	19	45	14	50	16	0.76	0.48
Total accuracy delayed red X (%)	83	13	79	8	84	10	0.74	0.49
1st 8 minutes accuracy blue X (%) †	47	18	52	11	53	19	-	-
1st 8 minutes accuracy delayed red X (%)	78	14	71	13	78	16	-	-
2nd 8 minutes accuracy blue X (%) †‡	36	22	38	17	47	20	-	-
2nd 8 minutes accuracy delayed red X (%)	87	13	86	8	90	8	-	-
RT correct blue X (ms)	581	34	587	30	579	19	1.24	0.302
RT incorrect delayed red X ms	551	23	562	26	548	17	1.25	0.298
Discriminability red X	0.72	0.10	0.71	0.09	0.78	0.06	2.52	0.097
Bias red X	−0.14	0.13	−0.17	0.08	−0.10	0.14	1.01	0.377
Discriminability non-X	0.84	0.05	0.84	0.04	0.86	0.04	1.01	0.375
Bias non-X	0.12	0.03	0.12	0.05	0.14	0.03	1.20	0.316

† Repeated measures ANOVA revealed a significant main effect of trial time for red X ($F = 15$, P 0.001) trials. There were no between group differences across trial time (group × time $F = 0.9$, $P = 0.42$).

‡ Repeated measures ANOVA revealed a significant main effect of trial time for blue X ($F = 37$, P 0.001) trials. There were no between group differences across trial time (group × time $F = 1.0$, $P = 0.39$).

ADHD, attention-deficit hyperactivity disorder; BPD, bipolar disorder; SD, standard deviation.

TABLE 3.

Regions of significant brain activation in each of the three group comparisons

Region of interest	Activation	Laterality	Brodmann area(s)	Centre of mass talairach coordinates (X, Y, Z)			Volume (3-mm³ voxels)
Bipolar versus healthy							
Cerebellar vermis	Decreased	Bilateral		-2.6	-33	-31	505
Parahippocampal gyrus, hippocampus, amygdala	Decreased	Left		-37	-9	-18	429
Postcentral gyrus	Decreased	Left		-42	-9	48	426
Precentral gyrus	Decreased	Right		58	-7	32	310
Middle and superior temporal gyrus	Increased	Right	22	52	-50	15	254
Fusiform gyrus, inferior temporal gyrus	Decreased	Right	20	44	7	-26	167
ADHD versus healthy							
Anterior cingulate	Decreased	Left	24	-3	30	2	256
Superior temporal gyrus	Increased	Left	42, 22	-64	-17	12	174
Insula	Increased	Right		30	-11	20	169
ADHD versus bipolar							
Superior temporal gyrus, insula	Increased	Left	22	-53	-6	11	630
Cuneus, posterior cingulate	Increased	Right	31, 30, 18	21	-70	11	250
Middle occipital gyrus, lingual gyrus, cuneus	Increased	Left	30	-38	-64	10	245

All regions were significantly at P 0.05 and with a cluster-level correction of 137 contiguous voxels.

ADHD, attention-deficit hyperactivity disorder