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Decreased anterior cingulate activation in a motor task in youths with bipolar disorder

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Abstract

Background—Bipolar disorder (BP) is characterized by abnormal shifts in mood between episodes of mania and severe depression, both of which have been linked with psychomotor disturbances. This study compares brain activation patterns in motor networks between euthymic youths with BP and healthy controls (HC) during completion of a simple motor task.

Methods—35 youths with BP and 35 HC (aged 10–19) completed a self-paced sequential bilateral finger tapping task, consisting of a 4-minute scan block with alternating 20 second periods of either the tapping task (6 blocks) or rest (6 blocks), while undergoing functional magnetic resonance imaging. Clinical and behavioral symptoms were assessed using the Child Behavior Checklist (CBCL). A between group whole brain analysis compared activation pattern differences while controlling for effects of age and sex. Clusters meeting whole-brain false discovery rate (FDR) correction ($qFDR < .05$) were considered statistically significant. *Post hoc* analyses evaluating comorbid attention-deficit/hyperactivity disorder (ADHD) in the BP group were also conducted.

Results—Significantly decreased activation was found in the anterior cingulate cortex (ACC) in youths with BP compared to HC. Furthermore, ACC activation was negatively correlated with CBCL mood dysregulation profile scores in the BP group. No significant differences in functional activation patterns were found between youths with BP and comorbid ADHD and those with only BP.

Conclusions—These findings suggest a potential common mechanism of impaired ACC modulation between emotion dysregulation and motor processing in youths with BP.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Keywords

bipolar disorder; adolescents; fMRI; finger tapping; anterior cingulate

Introduction

Pediatric bipolar disorder (BP) is primarily a disorder of mood regulation and is often characterized by abnormal shifts in mood that fluctuate between episodes of mania and severe depression, both of which display particular patterns of psychomotor disturbance (Frankland et al., 2015). Indeed, one recent study suggested that psychomotor agitation may be a key indicator of a BP diagnosis in depressed patients (Iwanami et al., 2015). Complicating matters is the high percentage of youths with BP that manifest comorbid diagnoses, such as attention-deficit/hyperactivity disorder (ADHD), which frequently present with overlapping symptom profiles (Joshi & Wilens, 2009; Marangoni, De Chiara, & Faedda, 2015) such as psychomotor agitation and fluctuations in mood (Skirrow, McLoughlin, Kuntsi, & Asherson, 2009). Despite the well characterized overlap in brain regions responsible for motor and mood regulation, little is known regarding the relationship between mood dysregulation inherent to BP and simple motor circuit activation regardless of whether it be related to motor agitation or motor retardation. Moreover, much of what we do know related to motor function in BP focuses on motor inhibition related tasks, which are primarily intended to assess cognitive processes, not basic motor function. For example, Deveney et al. (2012) used a stop signal functional magnetic resonance imaging (fMRI) task to compare activation patterns between youths with BP, ADHD, severe mood dysregulation (SMD), and healthy controls (HC). They found decreased activation related to failed inhibition in the anterior cingulate cortex (ACC) and right nucleus accumbens in youths with BP compared to HC and SMD. An additional exploratory analysis suggested that the decreased ACC activation may be independent of comorbid ADHD. In another study that used a Go/NoGo task to assess response inhibition, youths with BP demonstrated increased activation in the right dorsolateral prefrontal cortex (DLPFC) compared to HC. Interestingly, there were no significant performance differences between groups related to response inhibition on NoGo trials (Singh et al., 2010). Differences in the functional relationship between motor inhibition and BP diagnosis also appear to vary across development. For instance, Weathers and colleagues (2012) found opposing patterns of ACC dysfunction in youths and adults with BP compared to HC during a failed inhibition task such that ACC activation was increased in adults with BP and decreased in youths with BP compared to age matched HC suggesting divergent patterns of motor inhibition development between individuals with BP and HC. A simple bilateral self-paced sequential finger tapping task has been used to study basic motor circuit abnormalities in a variety of developmental disorders in children and adolescents. For instance, using a finger tapping task completed during fMRI scanning, Mostofsky et al. (2006) compared activation patterns in children with ADHD to those of HC and found significantly decreased activation in primary motor cortex in the ADHD group suggesting possible anomalous cortical system development. It has been suggested that using a simple motor task to investigate the pathophysiology of BP may mitigate between group differences related to cognitive differences as opposed to simple motor circuit differences (Marchand, Lee, Thatcher, Jensen, et al., 2007). Furthermore,

recent evidence suggests dysfunctional manual motor speed, assessed using a finger tapping test, may be considered an endophenotype of BP (Correa-Ghisays et al., 2017). To date, use of a simple motor task has not been used to study motor circuit abnormalities in youths with BP. Also of interest is whether or not the functional consequences of mood dysregulation affects motor circuits.

A number of neuroimaging studies have examined the relationship between symptoms of mood dysregulation and BP. Indeed, mania, a principal diagnostic symptom in BP, has been associated with impaired inhibitory control related to ventrolateral prefrontal (VLPFC), ventromedial prefrontal, and ACC dysfunction (Altshuler et al., 2005; Mazzola-Pomietto, Kaladjian, Azorin, Anton, & Jeanningros, 2009). Moreover, in youths with BP, resting-state fMRI studies have reported altered regional homogeneity in ventral-affective and dorsal-cognitive circuits (Xiao et al., 2013), decreased connectivity between the right superior temporal gyrus and left DLPFC (Dickstein et al., 2010), and between the amygdala and the hippocampus and precentral gyrus (Singh, Kelley, Chang, & Gotlib, 2015), and increased connectivity between the amygdala and the precuneus when compared to HC (Singh et al., 2015). Taken together, these findings suggest that the neural circuits related to mood dysregulation in BP appear to be dispersed throughout the brain and may also affect motor circuits.

Based on previous studies that have described both motor agitation and motor retardation in patients with BP (Frankland et al., 2015; Iwanami et al., 2015; Sobin, Mayer, & Endicott, 1998), as well as the diffuse circuits related to mood dysregulation (Dickstein et al., 2010; Singh et al., 2015; Xiao et al., 2013), we tested whether or not youths with BP would demonstrate differential activation patterns compared to HC when completing a self-paced sequential bilateral finger tapping fMRI task. We expected to see significantly decreased activation in frontostriatal related regions in BP compared to HC. Moreover, we predicted that these differences in activation patterns would relate to higher levels of emotion dysregulation within the BP group. We tested these predictions first by performing a between-group comparison intended to evaluate how a BP diagnosis impacts activation patterns, and second, by examining how these differences related to variable patterns of emotion dysregulation in the BP group. Due to the complexity of the circuits involved, a whole-brain analysis approach was used. Additionally, owing to the high occurrence of youths with a dual diagnosis of BP and ADHD, we also performed *post hoc* analyses comparing youths with BP and comorbid ADHD (BP+ADHD) to those with a diagnosis of BP only (BP-ADHD). Finally, we correlated our fMRI findings with measures from the Child Behavior Checklist (CBCL), which is one of the best-studied, empirically derived, parent-report assessments that measures behavioral and emotional problems related to psychopathology in children (Achenbach & Rescoria, 2001). In addition to providing a wealth of information related to specific symptoms of psychopathology, the CBCL also provides symptom profile scores related to internalizing and externalizing behaviors as well as an overall total symptom profile score (Cohen, Gotlib, Kershner, & Wehrspann, 1985). In a preliminary meta-analysis investigating the characterization of youths with pediatric BP, elevated attention problems, anxious/depressed, and aggression subscale scores were found to be consistent in children diagnosed with BP (Mick, Biederman, Pandina, & Faraone, 2003). This cluster of behavior problems has been referred to as the Child Behavior

Checklist Dysregulation Profile (CBCL-DP) (Althoff, Rettew, Ayer, & Hudziak, 2010; Ayer et al., 2009). We therefore also utilized this composite measure in correlational analyses in this study.

Methods

Participants

Following approval by the Institutional Review Board at the University of Utah, a total of 70 subjects, including 35 youths with BP and 35 HC youths, were recruited from the community through local advertising. Groups were matched for sex, age, and full-scale intelligence quotient (FSIQ). Inclusion criteria for study participants consisted of the following: male or female, 10–19 years of age, and of any race or ethnicity. Parental or legal guardian consent was required of all study participants under the age of 18. All study participants provided written informed assent or consent prior to study participation. A clinical and diagnostic semi-structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL) (Kaufman et al., 1997) was conducted for each study participant under the age of 18 by a board-certified child psychiatrist (MLL). For participants 18 and older, the Structured Clinical Interview for DSM-IV Patient Version (SCID-P) was used in tandem with the ADHD module from the K-SADS-PL-W (First, Spitzer, Gibbon, & Williams, 1996; Kaufman et al., 1997). Inclusion criteria for BP subjects included a DSM-IV-TR diagnosis of Bipolar Disorder, Type I, currently euthymic. Healthy control participants had no current or past history of a DSM-IV-TR Axis I diagnosis. Exclusion criteria for both groups included: FSIQ < 70, autism, schizophrenia, conduct disorder, eating disorder, drug or alcohol dependence, major sensorimotor handicaps, active neurological or medical disease, pregnancy, metal fragments or implants, a history of claustrophobia, or any other MRI scan contraindications. Familial history of psychiatric disorders was obtained from the parents of study participants. Youths with BP were allowed to continue currently prescribed medications with the exception of stimulant medications. Participants were required to stop stimulant medications at least 24 hours prior to scanning.

Internalizing and externalizing symptoms, common in children and adolescents with BP, were assessed using the CBCL (Achenbach & Rescoria, 2001). A dysregulation profile score (CBCL-DP) was also computed for each subject by adding the raw scores from the CBCL attention problems, aggressive behavior, and anxious/depressed subscales (Althoff et al., 2010; Ayer et al., 2009). The Wechsler Abbreviated Scale of Intelligence (WASI) was used to assess FSIQ (Wechsler, 1999). Measures of current psychopathology were obtained using the Child Depression Rating Scale – Revised (CDRS) (Poznanski et al., 1984) and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). Finally, the ADHD Rating Scale (ARS) was used to assess impulsivity/hyperactivity and inattention related symptoms (DuPaul, 1998).

Imaging Data

Imaging data were acquired at the Utah Center for Advanced Imaging Research (UCAIR) using a 3.0-T Siemens Trio scanner. Each subject completed a structural scan obtained using

a T1-weighted 3D MPRAGE sequence acquired sagittally using a 12-channel head coil with TE/TR/TI=3.38ms/2.0s/1.1s, 8° flip, 256×256 acquisition matrix, 256 mm² FOV, 160 slices, 1.0 mm slice thickness, generalized autocalibrating partially parallel acquisition with acceleration factor (GRAPPA)=2. Blood oxygen level dependent (BOLD) echo-planar images (TR=2.0 seconds, TE=28 ms, 40 slices at 3 mm section thickness, FOV=220 mm²) were obtained while participants engaged in a self-paced bilateral finger tapping task consisting of a 240 second scanning block with alternating 20 second periods of either the tapping task (6 blocks) or rest (6 blocks). Participants were instructed to bilaterally tap their thumb with each finger sequentially and continuously when prompted by the word “start” on the screen. The bilateral thumb-to-finger tap was self-paced and monitored via a closed-circuit television to ensure compliance. If participants were noted to be performing the task incorrectly, the imaging sequence was stopped and subsequently restarted after the participant was re-educated on the proper technique. Only scans that include successful task compliance by direct visual inspection are included in this study. Participants’ MRI scans were reviewed by a board-certified CAQ neuroradiologist to rule out structural pathology.

Preprocessing of BOLD fMRI data was performed in Matlab (MathWorks, Natick, Massachusetts) using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK). A field map sequence was acquired for all subjects and used to correct for magnetic field distortion during image acquisition. All images were then corrected for motion using a realign and unwarp procedure. Each subject’s BOLD images were coregistered to their individual MPRAGE anatomic image sequence, segmented by tissue type (gray matter, white matter, and cerebral spinal fluid), normalized to the Montreal Neurological Institute template brain, and smoothed using a 6-mm kernel. A general linear model was used to create activation maps for each subject using individualized motion correction parameters as a regressor and Task>Rest as a contrast. A second-level random-effects analysis was then performed for the BP and HC subjects using the t-contrast images from each subject and age and sex as covariates. Examples of group specific activation and conjunction maps can be viewed in Figure 1 with details related to activation clusters in found in Table S1. Images were created using BrainNet Viewer (Xia, Wang, & He, 2013).

Data Analyses

Only clusters that are false discovery rate (FDR) corrected at $qFDR < .05$ across the whole brain are reported as significant in study figures, with cluster-defining threshold of $p < .001$. The SPM Anatomy toolbox (Eickhoff et al., 2005) was used to identify anatomical region location based on MNI coordinates. Additional *post-hoc* two-sample t-test analyses were conducted comparing BP-ADHD with BP+ADHD and comparing activation patterns between groups using FSIQ as a covariate in order to rule it out as a confounding factor. Medication status was also accounted for using the same method when comparing BP with and without a comorbid ADHD diagnosis.

Statistical analyses were conducted using SPSS software (version 23) for Mac OS X. Two-sample t-tests and chi-square tests were performed for demographic and clinical variables. BOLD contrast percent change values were extracted from significant clusters identified in the second-level random-effects analysis, comparing HC and BP subjects, using MarsBaR

(Brett, Anton, Valabregue, & Poline). Pearson correlation coefficients were performed between BOLD values and clinical variables including externalizing, internalizing, total and dysregulation profile scores from the CBCL.

Results

Demographic and Clinical Results

All study participants included in the BP group met DSM-IV-TR diagnostic criteria for Bipolar Disorder, Type I. Of the 35 BP subjects, 11 also met diagnostic criteria for ADHD. Twenty-five of the BP participants were currently taking one or more psychotropic medications including mood stabilizers ($N = 20$), atypical antipsychotics ($N = 15$), antidepressants ($N = 11$), lithium ($N = 3$) stimulants ($N = 7$), and/or nonstimulant medications (guanfacine) ($N = 1$). Diagnostic groups were matched for sex, age and FSIQ (see Table 1). Symptoms of depression and mania as well as impulsivity/hyperactivity and inattention were significantly increased in BP relative to HC. However, all participants with BP were euthymic at the time of the study. Furthermore, internalizing, externalizing, total problems score, and dysregulation profile scores on the CBCL were also significantly increased in the BP group compared to HC.

Finger Tapping Task Group Analysis

All fMRI analyses compared activation patterns between groups in terms of Task>Rest with sex and age being included as covariates. Separate one-tailed t-tests for both BP and HC groups indicated significant activation in bilateral primary and supplementary motor areas (see Figure 1 and Table S1). Between group analyses indicated a pattern of significantly decreased activation in the BP group relative to controls in the bilateral rostral ACC (see Figures 2, 3 and Table 2). No significant differences were found between BP-ADHD and BP +ADHD. All between group analyses remained significant when controlling FSIQ. A *post hoc* analysis comparing BP-ADHD and BP+ADHD while controlling for medication status also found no significant differences between groups. No significant between-group differences were evident in premotor, primary motor, or supplementary motor areas in any of the analyses. Finally, the BP group showed no significantly increased activation in any area when compared to HC.

Pearson correlation coefficients were computed using behavioral and emotion regulation variables and BOLD percent signal change values extracted from the cluster located in the ACC. Significant negative correlations were found between rostral ACC activation and CBCL total ($r = -.439$, $p = .013$) and dysregulation profile ($r = -.388$, $p = .031$) scores in the BP group. No significant correlations were found between BOLD percent signal change in the ACC cluster and CBCL internalizing, externalizing, YMRS, CDRS, or ARS scores in the BP group. No significant correlations were found between behavioral and emotion regulation variables in the HC group.

Discussion

This is the first study to use a self-paced sequential bilateral finger tapping task to assess neural activation patterns in pediatric BP. We found that relative to HC, youths with BP

demonstrated decreased activation in the bilateral ACC, which was associated with increased symptoms of mood dysregulation in youths with BP. Although there are no prior studies examining a simple finger-tapping task in youths with BP, similar studies have been performed in adults with BP and findings conflict with our current study. For instance, in an fMRI study comparing 10 adults with BP to 10 matched controls, no significant between-group activation differences were found when employing a similar finger tapping task (Yoshimura et al., 2014). As part of a longitudinal study conducted with 10 adult males with BP, subjects completed a paced motor activation task consisting of alternating 15 second periods of rest or button pressing using the thumb for both left and right hands (Marchand, Lee, Thatcher, Thatcher, et al., 2007). The task was completed when the subjects were in a depressed state, and again when euthymic. When analyzing activation pattern differences between mood states, greater activation was reported in the right ACC and medial frontal gyrus in the euthymic state compared to the depressed state. Differences between the current study and prior adult studies could be related to smaller sample sizes, gender selection and age. However, despite these differences our current study and the study performed Marchand et al. did find ACC activation differences that were associated with mood dysregulation.

Due to the functional heterogeneity of the ACC, it has been linked with a large number of distinctive functions including motor control, emotion processing, and a number of cognitive processes (Bush, Luu, & Posner, 2000). Several fMRI task related findings also suggest a role for the ACC in BP. For instance, negative activation patterns in the ACC were reported in BP compared to HC during completion of a Stroop task (Gruber, Rogowska, & Yurgelun-Todd, 2004), whereas increased bilateral ACC activation was reported in BP compared to HC in a group of children and adolescents while performing a 2-back visuospatial working memory task (Chang et al., 2004). Resting-state fMRI studies have also reported abnormalities in ACC activation patterns related to mood dysregulation. For example, in a study comparing Chinese youths with BP related mania to age- and sex-matched HC, a significant positive correlation was reported between ACC activation and YMRS score (Xiao et al., 2013). Our simple-finger tapping task study provides further evidence of the role of the ACC in mood dysregulation in pediatric BP.

Several limitations should be considered when interpreting the findings in this study. Principally, this study included a limited sample size of individuals with both BP and ADHD making direct comparisons between the three groups impractical due to limited power. Ideally, a matched BP and ADHD sample would be compared with an additional ADHD only sample. Moreover, medication usage in the BP group was diverse and, although findings in the present study indicate no differences in activation patterns when comparing BP subjects with and without ADHD, even when controlling for medication effects, the true effects of comorbid ADHD and medication status remains uncertain. Our sample was required to be free from stimulant medication use 24 hours prior to scanning which may have unduly influenced the lack of differences between BP with and without ADHD. Previous studies have reported diffuse regions of decreased functional activation associated with inhibition related tasks in youths with ADHD, including decreased activation in the ACC (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). It is possible our main finding of decreased activation in the ACC in BP compared to HC is being influenced by the inclusion of youths with BP and comorbid ADHD. Washout of stimulant medications may have led to

While visual confirmation of task execution was conducted, we were unable to directly compare the precise start/stop times and speed of which the finger tapping task was completed. As such, it may be that there was a mechanical difference in task completion between groups that may have influenced activation pattern differences. As previously mentioned, no scans were included in this analysis where visual confirmation was not available; however, the unavailability of more quantitative metrics of task compliance raises the possibility of type I and II errors. Additionally, despite our intention to focus on motor activation by using a self-paced finger tapping task with no distinct cognitive factor, our main finding was located in the rostral ACC as opposed to the dorsal ACC. This suggests that activation differences between groups may be more likely related to inhibitory processes related to the nature of the block design used for our task as opposed to simple motor activation.

In summary, this is the first study to use a self-paced sequential bilateral finger-tapping task to assess neural activation patterns in a large and well-described cohort of youths with BP.

We found that relative to HC, youths with BP demonstrated decreased activation in the bilateral ACC, which was associated with increased symptoms of mood dysregulation in youths with BP. Our findings suggest a link between emotion dysregulation and motor processing in youths with BP that may relate to rostral ACC dysfunction as a shared mechanism related to symptom clusters in bipolar disorder. Further studies examining the impact of mood state, including depression and mania, on ACC activation patterns utilizing a motor task will help to further clarify the biological underpinning of the mood dysregulation and psychomotor disturbances seen in BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Bipolar disorder (BP) is characterized by abnormal shifts in mood between episodes of mania and severe depression, both of which have been linked with psychomotor disturbances.
- This study found decreased activation in the rostral anterior cingulate cortex (ACC) in youths with BP compared to HC.
- This decreased ACC activation was associated with increased symptoms of mood dysregulation in the BP group.
- These findings suggest a potential common mechanism of impaired rostral ACC modulation between emotion dysregulation and motor processing in youths with BP.

Figure 1.

Task activation maps (task > rest) for (A) healthy controls (HC) and (B) youths with bipolar disorder (BP) indicating regions with peak BOLD activation patterns during the completion of a self-paced sequential bilateral finger tapping task. (C) Conjunction analysis indicating regions of activation overlap between HC and BP (blue), where only HC demonstrated increased activation in task > rest (red), and only BP showed increased activation (green).

Figure 2. Whole brain between-group fMRI results for self-paced sequential bilateral finger tapping task showing significantly increased activation patterns in healthy control youths compared to youths with bipolar disorder.

Figure 3. Boxplot representing significant BOLD contrast percent change values between healthy controls (HC) and youths with bipolar disorder (BP) extracted from cluster located in the anterior cingulate cortex (Figure 2).

Table 1

Clinical demographics with between-group differences

	HC (N=35)		BP (N=35)		χ^2
	N	%	N	%	
Sex (male)	17	48.60	15	42.90	ns
Current Psychotropic Therapy	–	–	25	71.43	–
	Mean	SD	Mean	SD	$p =$
Age (months)	181.31	24.17	188.51	23.71	ns
FSIQ	111.66	10.71	105.80	15.62	ns
CDRS ¹	17.50	2.43	23.91	5.03	<.001
YMRS ²	0.32	1.09	6.38	4.61	<.001
ARS Inattention ³	0.55	1.75	4.33	3.03	<.001
ARS Impulsivity/Hyperactivity ³	0.18	0.73	2.52	2.65	<.001
CBCL Anxious/Depressed ⁴	1.68	1.89	9.68	5.52	<.001
CBCL Attention Problems ⁴	1.62	2.41	9.06	3.92	<.001
CBCL Aggressive Behavior ⁴	2.21	2.95	10.35	7.37	<.001
CBCL Dysfunction Profile ⁴	5.50	5.73	29.10	13.07	<.001
CBCL Internalizing ⁴	4.21	3.88	20.81	11.52	<.001
CBCL Externalizing ⁴	3.59	4.14	17.65	11.02	<.001
CBCL Total ⁴	14.41	13.72	64.74	28.61	<.001

FSIQ = Full Scale IQ; CDRS = Children's Depression Rating Scale; YMRS = Young Mania Rating Scale; ARS = ADHD Rating Scale; CBCL = Child Behavior Checklist;

¹ HC=34, BP=33;² HC=34, BP=24;³ HC=33, BP=33;⁴ HC=34, BP=31

Table 2

Regions demonstrating increased BOLD activity in Task>Rest

Regions	K	T	x	y	z	<i>qFDR</i> _{-corr}
HC>BP						
R Anterior Cingulate Cortex	117	5.04	15	44	8	< .001
R Anterior Cingulate Cortex		4.34	3	35	-7	
L Anterior Cingulate Cortex		3.87	-3	35	11	
L Anterior Cingulate Cortex		3.77	-3	29	-1	

Bolded region indicates cluster maxima