Effects of acute aerobic exercise on neural correlates of attention and inhibition in adolescents with bipolar disorder

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Executive dysfunction is common during and between mood episodes in bipolar disorder (BD), causing social and functional impairment. This study investigated the effect of acute exercise on adolescents with BD and healthy control subjects (HC) to test for positive or negative consequences on neural response during an executive task. Fifty adolescents (mean age 16.54 ± 1.47 years, 56% female, 30 with BD) completed an attention and response inhibition task before and after 20 min of recumbent cycling at ~ 70% of age-predicted maximum heart rate. 3 T functional magnetic resonance imaging data were analyzed in a whole brain voxel-wise analysis and as regions of interest (ROI), examining Go and NoGo response events. In the whole brain analysis of Go trials, exercise had larger effect in BD vs HC throughout ventral prefrontal cortex, amygdala and hippocampus; the profile of these effects was of greater disengagement after exercise. Pre-exercise ROI analysis confirmed this ‘deficit in deactivation’ for BDs in rostral ACC and found an activation deficit on NoGo errors in accumbens. Pre-exercise accumbens NoGo error activity correlated with depression symptoms and Go activity with mania symptoms; no correlations were present after exercise. Performance was matched to controls and results survived a series of covariate analyses. This study provides evidence that acute aerobic exercise transiently changes neural response during an executive task among adolescents with BD, and that pre-exercise relationships between symptoms and neural response are absent after exercise. Acute aerobic exercise constitutes a biological probe that may provide insights regarding pathophysiology and treatment of BD.

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INTRODUCTION

Cognitive dysfunction is common among adolescents with bipolar disorder (BD) during and between mood episodes, contributing to social and functional impairment.1–3 Meta-analytic findings implicate attention and executive function as among the most impaired domains.2 Single bouts of aerobic exercise are clinically relevant because they can acutely improve cognition, mood processing, anxiety and smoking cessation,4–6 and because they can inform our understanding of mechanisms underlying the benefits of longer exercise interventions.7 Although reviews describe putative benefits of aerobic long-term exercise in BD,8–12 no studies have examined the impact of acute aerobic exercise on neural response during an executive task in BD.

Numerous studies among adults and youth with BD have examined neural activation for executive processes during sustained attention and inhibition,13–24 using Stop-signal14–16,18,22 or Go-NoGo17,19,21,24 tasks. Both tasks share a sustained attention component with repeated ‘Go’ response to a stimulus and maintenance of vigilance for a Stop cue or a NoGo stimulus. The implementation of these tasks have been varied, namely on the stop trial response instructions, ratios of inhibition trials, block or event analysis, and use of high-level or baseline fixation contrasts.23,25 Consequently, the literature has mixed results. Stop-signal designs are more likely to find latency or accuracy deficits in BDs,14–16,22 whereas only one study with a Go-NoGo design found any evidence of behavioral deficit.17 Brain regions showing difference in neural response between adolescents with BD and healthy controls (HC) were also quite variable. Consistent group differences did emerge in rostral anterior cingulate cortex (rACC),16,18,19,22,24 striatal reward system (caudate, putamen or accumbens)14,18,19,21,22,24 and ventral prefrontal cortex (vPFC).14,16,21,22 However, there is limited consensus in the literature regarding directionality. For the rACC, BDs showed decreased activation16,19,22 slightly more often than increases;18,24 For the striatum, BDs showed decrease14,21,22 and increase18,19,24 equally often. For vPFC, more stability was observed, in the form of decrease.14,16,21,22 In the current study, we chose to simplify potential inconsistencies by concentrating on task versus fixation contrasts.23,25

Potential physiological mechanisms of exercise-related reduction of cognitive symptoms in BD include availability of monoamines and endorphins, exercise-induced inflammatory response, reversal of oxidative stress, BDNF, epigenetics, neuroplasticity and cellular resilience.8–12,26 Studies demonstrating exercise effects on neurocognitive function in BD have been slow to emerge.11,12,26 However, there is a developing literature establishing improvement of neurocognitive function with long-term exercise in schizophrenia27,28 and depression,29 and chronic and acute exercise in ADHD.30

Although we know of no studies examining the effects of acute bouts of aerobic exercise on executive function with neuroimaging in psychiatric populations, a recent meta-analysis of healthy
participants found moderate intensity exercise improved executive function for individuals of all fitness levels from 14 to 64 years of age when testing occurred at least 11 min after exercise (in contrast to during or immediately after exercise). One neuroimaging study of acute exercise effects on healthy young female adults demonstrated activation increases in middle prefrontal, lingual and fusiform gyri and decreases in ventral PFC and ACC during an executive task (n-back) with stable behavioral performance following acute moderate intensity exercise. Two studies of acute exercise effects in ADHD using electrical evoked response potential found frontal amplitude changes after exercise for executive tasks. Two recent studies of chronic exercise effects are also worth mentioning. In the first study, children participating in a 9-month physical activity program demonstrated decreases in dorsal PFC activation but stable ACC activation while improving executive performance (Go-NoGo task). Finally, one imaging study on chronic exercise effects among adolescents with ADHD found that a combined methylphenidate and exercise program increased frontal lobe activation and decreased temporal lobe activity.

The current study tested the effects of an acute bout of exercise on neural response during sustained attention and inhibition. Based on previous reports, a Go-NoGo design is an optimal choice to minimize performance differences between BDs and HC. We used a high ratio of Go trials to increase sensitivity to the condition most likely to be matched for performance between groups. Two analyses were used. The first, whole brain analysis was used to assess exercise-related change in the two groups while accounting for regional and direction of difference, variability present in previous attention and inhibition studies of BD. The second analysis focused on two core regions that emerged in many of the studies reviewed, the rACC and the striatum; first testing for group differences pre-exercise, and then using these functionally defined loci to examine if exercise diminished or enhanced differences.

We hypothesized baseline and exercise-related differences in rACC, striatal and vPFC regions. Based on the literature review, we predicted that analyzing Go and NoGo scores relative to resting baseline in BD would confirm rACC is a node of deactivation deficit for Go trials; however, the literature did not allow us to anticipate the direction or trial locus of the striatum difference. The existing literature did not clearly suggest an anticipated direction of the exercise-related shift and a goal of this study was to find if acute exercise had positive or negative effect on brain response. Finally, exploratory analyses were used to provide context for symptom effects on rACC and striatal recruitment by testing the relationship of brain activity with mania and depression scores.

### Materials and Methods

Participants

Fifty-four adolescent participants (32 BD and 22 HC) were recruited. BD participants were recruited from the Centre for Youth Bipolar Disorder, a tertiary sub-specialty clinic at Sunnybrook Health Sciences Centre in Toronto. HC participants were recruited from the community via advertisements. Fifty participants (30 BD and 20 HC) were included in the behavioral and imaging analysis after excluding participants for excessive head motion (mean displacement >0.52 mm) or displacement spikes (>2 mm >4% of volumes). The study included English-speaking females and males, ages 13–20 years, who either: (1) met diagnostic criteria for BD I, II or not otherwise specified (symptom severity, comorbidities and current medications of the clinical sample are noted in Table 1); or (2) had no major or recent psychiatric disorders (no lifetime mood or psychotic disorders; no alcohol or drug dependence or anxiety disorders within 3 months) and no family history of BD or psychotic disorder (first- and second-degree relatives). Diagnoses were ascertained during semi-structured interviews with adolescents and parents using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). The KSADS Depression Rating Scale (DRS) and KSADS Mania Rating Scale (MRS) were used in place of the mood sections of the KSADS-PL. Participants’ current illness status was classified as hypomania (mania scores >12), depression (depression scores ≥13), mixed (both scores above threshold) or euthymia (both mania and depression scores below threshold). Full scale IQ as a composite of

### Table 1. Demographic and global functioning characteristics among adolescents with and without bipolar disorder (BD) and clinical characteristics of adolescents with BD

| BD (n = 30) | HC (n = 20) | Statistic | P-value |
|-------------|-------------|-----------|---------|
| **Demographics** | | | |
| Age | 16.8 ± 1.4 | 16.1 ± 1.5 | t = −1.8 | 0.08 |
| Female | 17 (57%) | 11 (55%) | X² = 0 | 0.91 |
| IQ* | 109 ± 11.3 | 113 ± 18.9 | t = 0.97 | 0.33 |
| Ethnicity (Caucasian) | 26 (87%) | 16 (80%) | X² = 0.4 | 0.53 |
| Socioeconomic status | 51.1 ± 13.0 | 55.3 ± 8.1 | t = 1.4 | 0.18 |
| Lives with both biological parents | 16 (53%) | 13 (65%) | X² = 0.8 | 0.41 |
| **Global functioning b** | | | |
| Maximum (past year) | 63.7 ± 11.8 | 91.0 ± 3.8 | t = 10.0 | < 0.001 |
| Current | 60.7 ± 10.9 | 90.8 ± 4.0 | t = 11.8 | < 0.001 |
| **BD clinical characteristics (n = 30)** | Mean ± s.d. | n (%) |
| **BD onset age** | 14.4 ± 2.4 | — |
| **BD subtype:** | | |
| BD-I | — | 10 (33.3) |
| BD-II | — | 10 (33.3) |
| BD-NOS | — | 10 (33.3) |
| Lifetime psychiatric hospitalization | — | 13 (54.2%) |
| **Symptom severity** | | |
| Mania² | 10.9 ± 9.6 | — |
| Depression² | 14.9 ± 11.9 | — |
| **Current illness phase** | | |
| Hypomania³ | — | 5 (16.7) |
| Depression³ | — | 7 (23.3) |
| Mixed³ | — | 8 (26.7) |
| Euthymia³ | — | 10 (33.3) |
| **Current Medications** | | |
| Second-generation antipsychotic | — | 21 (70.0) |
| Lithium or divalproex sodium | — | 6 (20.0) |
| Psychostimulant | — | 2 (6.7) |
| Antidepressant | — | 5 (16.7) |
| **Comorbidity (lifetime)** | | |
| Anxiety disorder | — | 19 (63.3) |
| ADHD | — | 14 (46.7) |
| ODD | — | 10 (33.3) |
| Conduct disorder | — | 3 (10.0) |
| Psychosis | — | 9 (30.0) |
| SUD | — | 9 (30.0) |

**Abbreviations:** ADHD, attention deficit hyperactivity disorder; BD, bipolar disorder; CGAS, children’s global assessment scale; DRS, KSADS depression rating scale; HC, healthy comparison group; MRS, KSADS mania rating scale; ODD, oppositional defiant disorder; SUD, substance use disorder; WASI, Wechsler abbreviated scale of intelligence. Variance (±) in s.d. Degrees of freedom for t = 48 and x² = 1. For HCs, clinical descriptors were limited to three (15%) individuals diagnosed with ADHD, with two (10%) reporting use of psychostimulants for medication. *Wechsler abbreviated scale of intelligence. **Children’s global assessment scale. †KSADS mania rating scale. ‡KSADS depression rating scale. §Hypomania, mania scores ≥12. £Depression, depression scores ≥13. ¶Mixed, both mania and depression scores above threshold. ©Euthymia, both mania and depression scores below threshold. Full scale IQ as a composite of
vocabulary and matrix reasoning scores was tested using the Wechsler Abbreviated Scale of Intelligence (WASI).40 Interviewers also administered the Children’s Global Assessment Scale (CGAS), which indicates participants’ level of general functioning,41 and the Family History Screen (with parents and adolescents) to identify the psychiatric status of first- and second-degree relatives.42 Participants and their guardians gave written informed consent and all procedures were approved by the institutional Research Ethics Board.

Procedure

Sustained attention to response task. Sustained attention to response task (SART) was used as a Go-NoGo style task.43,44 SART included 180 trials in 30 trial blocks separated by blocks of rest with additional jittered rest between each trial (E-prime v.1.2.1.94, Psychology Software Tools, Pittsburgh, PA, USA). The digits 1–9 were presented in pseudorandom order, with randomized font types and sizes. Each number was displayed for 250 ms followed by 900 ms of fixation. ‘Go’ trials consisted of the numbers 1, 2 and 4–9; ‘NoGo’ (inhibition) trials consisted of the number 3 (15% of trials). Each run consisted of seven blocks of rest (19.5 s in duration) interleaved with six trial blocks (34.5 s in duration) for a total experimental runtime of 5 min 43.5 s. Data were collected in two sessions, before and 25 min following exercise with pre-experiment practice to reduce learning effects.

Exercise. The exercise intervention consisted of 27 min of cycling on a stationary recumbent bicycle-ergometer (5 min of self-paced warm-up, 20 min of aerobic exercise and a 2-min cool down) with the goal of achieving 60–80% of the age-predicted maximal heart rate (HR) during exercise. Age-predicted maximal HR was defined as 220 beats-per-minute minus age in years.45 HR was recorded minute-by-minute and participants were instructed to adjust their performance if their HR deviated > 5 b.p.m. from the center of their target range (70% of max).

Imaging. Magnetic resonance imaging (MRI) data were collected with a 3 T Philips Achieva system (Philips Medical Systems, Best, The Netherlands) using body coil transmission and an eight channel head receive coil. Structural images were acquired via T1-weighted high resolution fast-field echo imaging (repetition time (TR)/echo time (TE))/inversion time (TI) = 9.5 - /2.3/1400 ms, spatial resolution 0.94 × 1.17 × 1.2 mm, 256 × 164 × 140 matrix, scan duration 8 min and 56 s). Functional gradient echo images using body coil transmission and an eight channel head receive coil. 3 T Philips Achieva system (Philips Medical Systems, Best, The Netherlands) were acquired at the group level using Harvard-Oxford cortical and subcortical structural atlases (P > 0.25); stereotaxic coordinates are reported in Talairach MNI space.46 Figures are reported in radiological convention (left = right). Whole brain analysis of SART response task group differences in Δ(pre-exercise) – (post-exercise) exercise effects; analysis of baselines and within-groups differences can be found in Supplementary Materials. Average % signal change from specific clusters for specific Harvard-Oxford labels (P > 0.25) were used to display pre- and post-exercise activation. Regions of interest analyses included bilateral rACC and striatum (caudate, putamen and accumbens) and were defined at the group level using Harvard-Oxford cortical and subcortical structural atlases (P > 0.25).47 rACC was segmented from ACC beginning one section anterior to termination of the hemispheric juncture of the corpus callosum.49–51 Within these ROIs, significant clusters of pre-exercise group differences were identified and peaks were used to display % signal change for pre- and post-exercise.

RESULTS

Clinical and aerobic response data

Groups were matched with respect to demographic variables (all P > 0.08; summary provided in Table 1). Mean HR during exercise was in the middle of the target range (70.0% of age estimated maximum overall; 69.7% BP, 70.5% HC, P = 0.66). HR exceeded the minimum of the target range for 90% of participants in at least 18 of the 20 min of aerobic activity.

SART behavioral performance

No univariate group or session differences were observed for Go trial performance or NoGo accuracy. See Table 2 for summary of univariate results and statistical tests. A multivariate ANOVA supported the univariate results (Pillais’ Trace = 0.085, F (3,46) = 1.4, P = 0.249, ηp² = 0.085, eigenvalue = 0.093).

Whole brain voxel-wise fMRI analysis

Baseline within-group effects, baseline group differences and within-group exercise effects from the whole brain analysis are described in Supplementary Results, Supplementary Tables S1 and S2, and Supplementary Figures S1 and S2. NoGo versus Go and NoGo correct versus NoGo incorrect contrasts were analyzed for exercise(4)) exercise for individual participants used ordinary least squares models. Group level analyses used mixed effects Flame 1 models. First-level contrasts included correct Go (hereafter ‘Go’), correct NoGo and incorrect NoGo trials separately, minus fixation. Incorrect Go trials were modeled but not analyzed. Activation was assessed for significance at α = 0.05, with family wise error cluster correction α = 0.05. Clusters were labeled using Harvard-Oxford cortical and subcortical structural atlases (P > 0.25); stereotaxic coordinates are reported in Talairach MNI space.46 Figures are reported in radiological convention (left = right). Whole brain analysis of SART response task group differences in Δ(pre-exercise) – (post-exercise) exercise effects; analysis of baselines and within-groups differences can be found in Supplementary Materials. Average % signal change from specific clusters for specific Harvard-Oxford labels (P > 0.25) were used to display pre- and post-exercise activation. Regions of interest analyses included bilateral rACC and striatum (caudate, putamen and accumbens) and were defined at the group level using Harvard-Oxford cortical and subcortical structural atlases (P > 0.25).47 rACC was segmented from ACC beginning one section anterior to termination of the hemispheric juncture of the corpus callosum.49–51 Within these ROIs, significant clusters of pre-exercise group differences were identified and peaks were used to display % signal change for pre- and post-exercise.

Table 2. Sustained attention to response task performance and ANOVA tables for adolescents with and without bipolar disorder

|               | Go RT | Go % Acc | NoGo % Err |
|---------------|-------|----------|------------|
| Pre-exercise  |       |          |            |
| BD            | 327 ± 79 | 96 ± 9.5 | 45 ± 26.1  |
| HC            | 326 ± 133 | 95 ± 7.9 | 44 ± 30.2  |
| Post-exercise |       |          |            |
| BD            | 319 ± 76 | 96 ± 6.8 | 44 ± 23.6  |
| HC            | 319 ± 127 | 92 ± 13.1 | 47 ± 26.5  |
| ANOVA        | F (ηp²) | P       | F (ηp²) | P |
| Group         | 0.1(0.01) | 0.991 | 0.8(0.01) | 0.374 | 0.1(0.01) | 0.941 |
| Session       | 1.0(0.02) | 0.334 | 2.7(0.05) | 0.104 | 0.2(0.01) | 0.697 |
| Group x session | 0.1(0.01) | 0.951 | 3.6(0.07) | 0.065 | 0.7(0.01) | 0.411 |

Abbreviations: ANOVA, analysis of variance; BD, bipolar disorder; HC, healthy comparison group. Variance (±) in s.d. Degrees of freedom = 1, 48.

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baseline group differences and within-group exercise effects for comparison to previous studies with high-level baselines. Significant clusters in these analyses were consistent with those observed in task versus fixation contrasts. The details of these results are described in Supplementary Results.

**Group effect on Δexercise brain response.** For Go trials, a group effect on Δexercise indicated more change in response to exercise for BDs > HCs including three clusters with peaks at left frontal orbital cortex (FOC; 6623 voxels, max Z = 4.62, peak = −20, 24, −22), right frontal pole (FP) extending to temporal pole (4028 voxels, max Z = 3.53, peak = 40, 20, −24), and right and left hippocampus (Hipp.) extending to posterior cingulate (2753 voxels, max Z = 3.55, peak = −16, −42, 2). This deactivation deficit in bipolar disorder (BD) relative to healthy controls (HC) was observed at regional peaks, extending to a relevant subcortical sub-cluster in amygdala (Amyg.). Evidence for deficit was not present following exercise. Error bars ± 1 s.e.

**Regions of interest fMRI analysis**

Pre-exercise group differences were found in left rACC (76 voxels, max Z = 2.45, peak = −8, 44, 0) for Go trials and in right accumbens (15 voxels, max Z = 2.86, peak = 6, 10, −2) for NoGo error trials. Figure 2a shows the pre-exercise difference cluster for Go and the bar plot shows a deactivation deficit for BDs relative to HCs; the pattern was toward reversal after exercise (F(1, 48) = 3.6, P = 0.065, $\eta^2 = 0.069$). For reference, NoGo error signal was also plotted and showed no pre-exercise difference but did increase after exercise. Figure 2b shows the pre-exercise difference cluster for NoGo and the bar plot shows an activation deficit; the pattern reversed after exercise (F(1, 48) = 8.6, P = 0.005, $\eta^2 = 0.152$). Reference to Go signal showed similarly reduced activation after exercise regardless of group. As a covariate control analysis, the effect of medication in relation to Go rACC and NoGo accumbens activation was analyzed. There was a non-significant trend toward greater deactivation deficit in rACC among BD participants taking antipsychotic medications. After accounting for antipsychotic medication, additional medication load was not a factor. Accumbens activity was unrelated to medication status. The details of these analyses are presented in Supplementary Results. Within the BD group, current mania and depression symptom scores did not correlate with pre-exercise activation in rACC (all P > 0.05). For accumbens (Figure 2b, bottom), greater depression scores were related to lower pre-exercise activation during NoGo errors ($r = −0.378$, $P < 0.05$) and greater mania scores were related to higher pre-exercise activation during Go trials ($r = 0.415$, $P < 0.05$); neither association was significant after exercise (all $P > 0.05$). In addition, illness status (hypomania, depression, mixed symptoms and euthymia) effects at baseline were examined. The subgroup samples were too small to analyze but descriptive data is provided in Supplementary Results. To summarize, BD subgroups showed patterns similar to the primary group, with the exception of weaker trends for depression for rACC and hypomania for accumbens. All groups showed similar exercise effect patterns.

**DISCUSSION**

This study investigated the effect of an acute bout of exercise on adolescents with BD to test for positive or negative consequences on neural response during an executive control task. A whole brain voxel-wise analysis of fMRI activation found between-group differences in exercise effects for BDs above HCs during sustained attention throughout vPFC and subcortical structures including the left FOC, and right FP, amygdala and hippocampus. An ROI analysis of baseline activation found pre-exercise group differences for Go trials in left rACC and for NoGo inhibition error trials in right accumbens. Comparison of individual differences in neural activity from rACC and accumbens to mania and depression symptoms for BDs found pre-exercise symptoms were associated with neural activity in accumbens before exercise but not following exercise. Collectively, these results supported our hypothesis that activation differences in response to acute exercise would be larger for BDs relative to HCs.

In the whole brain analysis of Go trials, HCs exhibited deactivation relative to rest before and after exercise. BDs, however, exhibited activity similar to rest, a deactivation deficit relative to HCs that was reversed after exercise. In ROI analysis of baseline Go trial activation, BDs demonstrated a deactivation deficit similar to the broader pattern found in the whole brain analysis. For reference, NoGo activation signal in the same rACC cluster showed no group effects pre-exercise, but did increase in BD after exercise. A different pattern was found for NoGo for a breakdown of these analyses. No differences were found on NoGo trials.

**Figure 1.** Whole brain group differences in Δexercise effect for performance-matched Go trial events. Differences in activation in three clusters with peaks in left frontal orbital cortex (FOC; 6623 voxels, max Z = 4.62, peak = −20, 24, −22), right frontal pole (FP) extending to temporal pole (4028 voxels, max Z = 3.53, peak = 40, 20, −24), and right and left hippocampus (Hipp.) extending to posterior cingulate (2753 voxels, max Z = 3.55, peak = −16, −42, 2). This deactivation deficit in bipolar disorder (BD) relative to healthy controls (HC) was observed at regional peaks, extending to a relevant subcortical sub-cluster in amygdala (Amyg.). Evidence for deficit was not present following exercise. Error bars ± 1 s.e.
inhibition errors wherein accumbens showed an activation deficit prior to exercise which was abolished after exercise. For reference, examination of Go activation in the accumbens cluster was similar for both groups, reducing after exercise. Finally, with respect to symptoms, the activation deficit on NoGo error trials was associated with higher depression scores. Mania scores were associated with more activation in response to sustained attention Go trials. After exercise no correlation was found for either measure.

Task performance, demographic variables and exertion were matched between BDs and HCs; in addition a series of covariate control analyses confirmed the stability of Δexercise effects when
accounting for BD subtype and a series of control variables. A secondary goal of the study was to use previously investigated ROIs to better characterize pre-exercise differences in activation both above and below baseline fixation without interpreting subtractive contrasts between attention and inhibition. A third area of interest was to understand how mania and depression symptoms may be related to exercise effects on neural response. Overall the results show that there was a combination of regionally specific deactivation and activation deficits in BD, the latter of which were also related to BD symptoms, with all results indicating reduction of these differences after an acute bout of aerobic exercise.

A recent study of functional connectivity during resting state in BD suggested dysbalance between DMN and other networks may explain core components of depression and mania phases of the disease.45 Specifically, in resting state, a deficit in PFC inter-network coupling leads to an over-active DMN and depression symptoms; a deficit in DMN intra-network coupling leads to under-active DMN and mania symptoms. In this context, the deactivation deficit observed here may be interpreted as a signature of this former, DMN dominance effect. Supporting this dysbalance interpretation, adolescents with BD failed to activate the accumbens during NoGo response, a pattern that, following exercise, changed along with the change in rACC deactivation deficit. Accumbens is a key node of the salience network responsible for dynamic switching between DMN and executive functions.68,69 As such, present findings suggest that failure or delay in switching between these functions is potentially a core mechanims in the etiology of the often reported BD inhibition deficit.

When deactivation deficit is used as the basis for a subtractive analysis with inhibition trials this will complicate interpretation of effects7–25 and may place the emphasis of models of BD attention and inhibition dysfunction on the inhibition component of response. The current data suggests ventral and medial PFC regions are implicated in dysfunction of sustained attention associated with a dominant DMN component that persists beyond resting state into an active attention task. Further investigation of functional coupling of DMN and other resting state networks and if the changes in this dysbalance do occur after exercise may be important for better understanding the relationship between mood symptoms and brain response during both attention and inhibition in BD.

Methodological limitations of these findings will now be addressed. There was no session-related control condition, and despite a pre-scanner practice session learning effects remain possible. However, as expected based on the task selected, no significant session effects were observed on behavior. Furthermore, interest in the consequences of acute exercise effects motivated this study, precluding the use of multi-day designs. The current study included a real-life heterogeneous clinical sample, as this is the population in which we foresee aerobic exercise serving as a potential therapeutic approach. Sensitivity analyses that interrogated ADHD comorbidity, current mood symptoms, BD-subtypes and medication status yielded largely convergent findings to the primary analysis (see Supplementary Results).

Finally, the influence of pharmacotherapy in this heterogeneous clinical sample must be considered.

**CONCLUSIONS**

The potential of aerobic exercise as adjunctive therapy in the treatment of adolescent BD is well-known. Here, we endeavored to better understand the effects of an acute bout of exercise on the neurophysiology of a commonly used experimental model of cognitive dysfunction that incorporates executive attention and inhibition processes known to be compromised in BD. We found evidence that a single 20-min bout of aerobic exercise impacts both neural deactivation deficits in attention and activation deficits in inhibition. Improved understanding of the acute effects...
of aerobic exercise, as well as between-group differences in this regard between BDs and HCs, may inform our understanding of the therapeutic mechanisms of aerobic exercise, as well as unique aspects of neurophysiological response to exercise in BD. Future investigations are needed to better understand the impact of salient clinical characteristics (for example, symptom status) on the observed findings, and, given the brief timeframe of the current study, to determine the duration of the observed effects.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1. Pavuluri MN, Schenkel LS, Aryal S, Harral EM, Hill SK, Herbener ES et al. Neurocognitive function in unmedicated manic and medicated euthymic pediatric bipolar patients. Am J Psychiatry 2006; 163: 286–293.
2. Joseph MF, Frazier TW, Youngstrom EA, Soares JC. A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2008; 18: 595–605.
3. Horn K, Roessner V, Holtmann M. Neurocognitive performance in children and adolescents with bipolar disorder: a review. Eur Child Adolesc Psychiatry 2011; 20: 433–450.
4. Daniel J, Cropley M, Ussher M, West R. Acute effects of a short bout of moderate versus light intensity exercise versus inactivity on tobacco withdrawal symptoms in sedentary smokers. Psychopharmacology (Berl) 2004; 174: 320–326.
5. Streith A, Feller C, Onken M, Godemann F, Heinz A, Dimeo F. The acute antipanic activity of aerobic exercise. Am J Psychiatry 2005; 162: 2376–2378.
6. Tian Q, Smith JC. Attentional bias to emotional stimuli is altered during moderate-versus light intensity exercise versus inactivity on tobacco withdrawal symptoms. Brain Res 2008; 1219: 87–96.
7. Thomason D, Turner A, Launder S, Giggler ME, Berk L, Singh AB et al. A brief review of exercise, bipolar disorder, and mechanistic pathways. Front Psychol 2015; 6: 147.
8. Syliva LG, Ametrafo NM, Nierenberg AA. Exercise treatment for bipolar disorder: potential mechanisms of action mediated through increased neurogenesis and decreased allostatic load. Psychopharmacology (Berl) 2020; 237: 178–197.
9. Leistung D, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH et al. Neural circuitry engaged during successful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 2007; 164: 52–60.
10. Leisengart E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH et al. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. Psychiatry Res 2010; 181: 36–43.
11. Singh MK, Chang KD, Mazaika P, Garrett A, Adleman N, Kelley R et al. Neural correlates of response inhibition in pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2010; 20: 15–24.
12. Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Pine DS et al. Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. Biol Psychol 2012; 89: 148–155.
13. Fleck DE, Elissen JC, Durling M, Lamy M, Adler CM, DeBello MP et al. Functional MRI of sustained attention in bipolar mania. Mol Psychiatry 2012; 17: 325–336.
14. Strakowski SM, Adler CM, Almeida J, Altschuler LL, Blumberg HP, Chang KD et al. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord 2012; 14: 313–325.
15. Townsend JD, Bookheimer SY, Roland-Loss CC, Moody TD, Eisenberger NI, Fischer JS et al. Deficits in inferior frontal cortex activation in euthymic bipolar disorder patients during a response inhibition task. Bipolar Disord 2012; 14: 442–450.
16. Weathers JD, Stringaris A, Deveney CM, Brotman MA, Zarate CA Jr, Connolly ME et al. A developmental study of the neural circuitry mediating motor inhibition in bipolar disorder. Am J Psychiatry 2012; 169: 633–641.
17. Fernández-Cocueria P, Salvador R, Monté GC, Salvador Sarró S, Goikolea JM, Arnall B et al. Bipolar depressed patients show both failure to activate and failure to de-activate during performance of a working memory task. J Affect Disord 2013; 148: 170–178.
18. Diler RS, Pan LA, Segreti A, Ladouceur CD, Forbes E, Cela SR et al. Differential anterior cingulate activity during response inhibition in depressed adolescents with bipolar and unipolar major depressive disorder. J Can Acad Child Adolesc Psychiatry 2014; 23: 10–19.
19. Pomarol-Clotet E, Salvador R, Sarró S, Gomar J, Vila C, Martínez A et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychol Med 2008; 38: 1185–1193.
20. Schuch FB, da Silveira LE, de Zenit TC, da Silva DP, Wollenhaupt-Aguirau B, Ferrari P et al. Effects of a single bout of maximal aerobic exercise on BDNF in bipolar disorder: a gender-based response. Psychiatry Res 2015; 229: 57–62.
21. Kintz M, Vakhroshcheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S et al. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. Schizophr Bull 2015; 41: 859–868.
22. Malchow B, Keller K, Hasen A, Dörfler S, Schneider-Axmann T, Hillmer-Vogel U et al. Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiphase schizophrenia patients. Schizophr Bull 2015; 41: 847–858.
23. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
24. Rommel A-S, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. J Am Acad Child Adolesc Psychiatry 2013; 52: 900–910.
25. Chang YK, Labban JD, Gapper JI, Etien JG. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res 2012; 1453: 87–101.
26. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
27. Rommel A-S, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. J Am Acad Child Adolesc Psychiatry 2013; 52: 900–910.
28. Chang YK, Labban JD, Gapper JI, Etien JG. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res 2012; 1453: 87–101.
29. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
30. Rommel A-S, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. J Am Acad Child Adolesc Psychiatry 2013; 52: 900–910.
31. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
32. Rommel A-S, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. J Am Acad Child Adolesc Psychiatry 2013; 52: 900–910.
33. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
34. Rommel A-S, Halperin JM, Mill J, Asherson P, Kuntsi J. Protection from genetic diathesis in attention-deficit/hyperactivity disorder: possible complementary roles of exercise. J Am Acad Child Adolesc Psychiatry 2013; 52: 900–910.
35. Cooney G, Dwan K, Mead G. Exercise for depression. Cochrane Database Syst Rev 2014; 3: CD003186.
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43 Robertson IH, Manly T, Andreade J, Baddeley BT, Yiend J. “Oops!”: Performance correlates of everyday attentional failures in traumatic brain injury and normal subjects. Neuropsychologia 1997; 35: 747–758.

44 Dutilh G, van Ravenzwaaij D, Nieuwenhuis S, van der Maas HLJ, Forstmann BU, Wagenmakers E-J. How to measure post-error slowing: a confound and a simple solution. J Math Psychol 2012; 56: 208–216.

45 Londeree BR, Moeschberger ML. Effect of age and other factors on maximal heart rate. Res Q Exerc Sport 1982; 53: 297–304.

46 Avants BB, Yushkevich P, Pluta J, Minkoff D, Korczykowski M, Detre J et al. The optimal template effect in hippocampus studies of diseased populations. Neuroimage 2010; 49: 2457–2466.

47 Avants BB, Tuition NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 2011; 54: 2033–2044.

48 Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004; 23: S208–S219.

49 Fornito A, Whittle S, Wood SJ, Velakoulis D, Pantelis C, Yucel M. The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. Neuroimage 2006; 33: 843–854.

50 McCormick LM, Ziebell S, Nopoulos P, Cassell M, Andreassen NC, Brumme M. Anterior cingulate cortex: an MRI-based parcellation method. Neuroimage 2006; 32: 1167–1175.

51 Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B et al. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Arch Gen Psychiatry 2009; 66: 431–441.

52 Diler RS, Segreti AM, Ladouceur CD, Almeida JR, Birmaher B, Axelson DA et al. Neural correlates of treatment in adolescents with Bipolar Depression During Response Inhibition. Mary Ann Liebert, Inc.: 140 Huguenot Street, 3rd Floor New Rochelle, NY, USA. 2013.

53 Osby U, Brandt L, Correia N, Ekborn A, Sparen P. Excess mortality in bipolar and unipolar disorder in sweden. Arch Gen Psychiatry 2001; 58: 844–850.

54 Weeke A, Juel K, Vaeth M. Cardiovascular death and manic-depressive psychosis. J Affect Disord 1987; 13: 287–292.

55 Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord 2009; 11: 657–662.

56 Goldstein BI, Carneithon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease. Circulation 2015; 132: 956–966.

57 Zheng H, Liu Y, Li W, Yang B, Chen D, Wang X et al. Beneficial effects of exercise and its molecular mechanisms on depression in rats. Behav Brain Res 2006; 168: 47–55.

58 Marais L, Stein DJ, Daniels WMU. Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. Metab Brain Dis 2009; 24: 587–597.

59 Cousins DA, Butts K, Young AH. The role of dopamine in bipolar disorder. Bipolar Disord 2009; 11: 787–806.

60 Skriver K, Roig M, Lundbye-Jensen J, Pingel J, Helge JW, Kiens B et al. Acute exercise improves motor memory: exploring potential biomarkers. Neurobiol Learn Mem 2014; 116: 46–58.

61 Spanagel R, Herz A, Shippenberg TS. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc Natl Acad Sci USA 1992; 89: 2046–2050.

62 Kabli N, Nguyen T, Balboni G, O'Dowd BF, George SR. Antidepressant-like and anxiolytic-like effects following activation of the μ-δ opioid receptor heteromer in the nucleus accumbens. Mol Psychiatry 2014; 19: 986–994.

63 Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001; 98: 676–682.

64 Raichle ME. The brain’s default mode network. Annu Rev Neurosci 2015; 38: 433–447.

65 Magioncalda P, Martino M, Conio B, Escelsior A, Piaggio N, Presta A et al. Functional connectivity and neuronal variability of resting state activity in bipolar disorder-reduction and decoupling in anterior cortical midline structures. Hum Brain Mapp 2015; 36: 666–682.

66 Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci 2015; 16: 55–61.

67 Menon V. Salience Network. In: Toga AW (ed). Brain Mapping: An Encyclopedic Reference, vol 2. Academic Press: Elsevier, 2015, pp 597–611.

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