

Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2012 August 7; 38(2): 127–133. doi:10.1016/j.pnpbp.2012.02.014.

Striatal Dysfunction During Failed Motor Inhibition in Children at Risk for Bipolar Disorder

Christen M. Deveney, Megan E. Connolly¹, Sarah E. Jenkins², Pilyoung Kim, Stephen J. Fromm, Melissa A. Brotman, Daniel S. Pine, and Ellen Leibenluft

Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, U.S. Department of Health and Human Services

Abstract

Background—A better understanding of the neural underpinnings of bipolar disorder (BD) can be obtained by examining brain activity in symptom-free individuals at risk for BD. This study examined the neural correlates of motor inhibition in a sample of symptom-free youths at familial risk for BD.

Methods—19 euthymic youths with BD, 13 asymptomatic youths with a first-degree relative with BD, and 21 healthy comparison children completed the stop signal task in a 3T scanner.

Results—Children at familial risk for BD exhibited increased putamen activation during unsuccessful inhibition that distinguished them from both healthy and BD children. Youths with BD exhibited reduced activation of the right nucleus accumbens during unsuccessful inhibition as compared to the other participant groups.

Conclusions—Striatal activation patterns differ between youths at risk for BD and healthy comparison children during a motor inhibition task.

Keywords

motor inhibition; bipolar disorder; population at risk; magnetic resonance imaging

1. Introduction

Studies of the pathophysiology of bipolar disorder (BD) are complicated by the potentially confounding effects of prior episodes of mania and depression, pharmacological treatments, current mood state, and comorbid psychiatric illnesses. Studies of unaffected individuals at risk for BD remove many of these confounding factors. Since the typical age of onset of BD is late adolescence or early adulthood (Weissman et al., 1996), studies of youths at-risk for BD may be particularly informative because these individuals may still develop the illness. However, relatively little research has examined the performance of such at-risk youths on

Corresponding Author: Christen M. Deveney, Section on Bipolar Spectrum Disorders, Emotion and Development Branch, National Institute of Mental Health, 15K North Drive, MSC 2670, Bethesda, MD 20892-2670, USA. deveneycm@mail.nih.gov; phone: 1-301-451-9754; fax: 1-301-402-6100.

¹Ms. Connolly is now at the Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University.

²Ms. Jenkins is now at the University of Colorado School of Medicine

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors have no conflicts to disclose.

cognitive and emotional tasks. Those that exist suggest that, compared with healthy subjects, at-risk youths exhibit deficits on measures of face emotion processing, problem solving, working memory/interference, and sustained attention (Brotman, Guyer, et al., 2008; Brotman, Skup, et al., 2008; Brotman et al., 2009; Diwadkar et al., 2011; Doyle et al., 2009). Here, we examined neural activation during a motor inhibition task in youths with BD, unaffected youths with a first-degree relative with BD, and healthy volunteers (HV). We used a motor inhibition task because deficits in motor inhibition are closely tied to a number of symptoms of BD.

1.1. Motor Inhibition, BD youths, and At-Risk Populations

Many BD symptoms may reflect behavioral disinhibition, including: pressured speech, difficulty concentrating, psychomotor retardation, and increased engagement in risky and inappropriate activities (American Psychiatric Association, 2000). Tasks that require individuals to withhold a motor response (e.g., Stop Signal Task, Go/No Go paradigms) document impaired motor inhibition among BD youths (Passarotti et al., 2010; Peluso et al., 2007; Swan et al., 2001, 2003, 2004; c.f., Cerullo et al., 2009; Leibenluft et al., 2007; McClure et al., 2005). Difficulties inhibiting motor responses may contribute to some of the impairing symptoms of BD such as impulsivity and pressured speech.

While motor inhibition deficits have been observed in the unaffected adult relatives of BD patients (Bora et al., 2009), only one study has examined this domain in youths at risk for BD (Singh et al., 2009). Youths who exhibited subclinical symptoms of BD and had a parent with the illness exhibited impulsivity and difficulty inhibiting motor responses, relative to healthy comparison children with unaffected parents (Singh et al., 2009). However, because the at-risk youths were already exhibiting depressive symptoms, it is unclear whether the observed deficits were related to early stages of disease, or whether such deficits would also be present in a symptom-free, at-risk population.

1.2. Neural Underpinnings of Motor Inhibition Tasks

Successful motor inhibition involves the recruitment of the right ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), supplementary motor areas, striatum, and subthalamic nucleus (for review Aron, 2011; Chambers et al., 2009). Failure to inhibit a motor response has been associated with activation in the prefrontal cortex, posterior parietal cortex, ACC, and caudate (Padmala and Pessoa, 2010; Rubia et al., 2003). Studies of BD youths suggest that aberrant recruitment of this fronto-striatal circuitry may contribute to their motor inhibition deficits. Previous studies using variations of the stop signal task have reported hypoactivation of fronto-striatal circuitry during inhibition trials among BD youths. For example, Cerullo and colleagues (2009) observed hypoactivation of the precentral gyrus among BD youths during a continuous performance task that was modified to include a stop signal. Decreased left lateralized prefrontal (medial, middle, and inferior) and right pregenual ACC activation was observed among manic BD youths relative to healthy comparison children completing a block design of the Stop Signal Task (Passarotti et al., 2010a); these deficits may normalize following lamotrigine treatment (Pavuluri et al., 2010). Finally, a study by Leibenluft and colleagues (2007) documented reduced VLPFC, striatum, and ACC activation among BD youths during unsuccessful inhibition in the Stop Signal Task. Together, these data suggest that abnormalities recruiting fronto-striatal regions may hinder the ability of BD youths to appropriately inhibit motor responses, but the directionality of the activation patterns may depend on the motor inhibition paradigm. We are unaware of any studies that have examined the neural responses of unaffected youths at risk for BD in a motor inhibition task.

1.3. Present Study and Hypotheses

The primary goal of the present study was to compare neural activity engaged during successful and unsuccessful motor inhibition in youths at familial risk for BD (AR), youths with BD, and healthy comparison subjects. We limited our sample to euthymic BD youths in order to identify trait abnormalities. We chose the stop signal task because of its targeted assessment of prepotent motor inhibition responses and its extensive use in healthy and psychiatric populations. Based on prior studies (for review Aron, 2011; Chambers et al., 2009), we identified the VLPFC, ACC, and striatum as regions of interest (ROIs) and investigated activation patterns using three contrasts: (1) stop incorrect vs. stop correct; (2) stop correct vs. go; and (3) stop incorrect vs. go. We hypothesized that, during unsuccessful inhibition of motor responses, AR youths would exhibit hypoactivation in fronto-striatal regions relative to healthy children, but that this hypoactivation would be less severe than that of youths with BD. Because research on youths at risk for BD is limited, we conducted a secondary whole-brain analysis examining group differences in activation for the three contrasts mentioned above. Finally, we explored whether activation patterns differed if a participant was considered at risk because they had a sibling or a parent with BD.

2. Methods and Materials

2.1 Participants

Participants were recruited as part of an ongoing study on BD at the National Institute of Mental Health (NIMH). Advertisements for youth with BD were placed in the community and to patient advocacy groups. AR youths were also identified from such advertisements, from the families of youths in our ongoing study of pediatric BD, and from individuals participating in a study of adult bipolar disorder at NIMH. HV participants were recruited from community advertisements and from the NIH Clinical Research Volunteer Program. All procedures were approved by the NIMH IRB. Participants and their parents provided informed assent/consent prior to engaging in study procedures. Participants received \$100 for their participation.

Diagnostic status for all participants - including the parents of AR youths - was determined by structured clinical interviews (The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime (Kaufmann et al., 1997) for children and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (First et al., 2002) or the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) for adults. Mood ratings were completed with the BD youths within 48 hours of scanning, including the Young Mania Rating Scale (YMRS; Young et al., 1978) and Children's Depression Rating Scale (CDRS; Poznanski et al., 1979). All clinical diagnostic and mood ratings were conducted by a Master's level or above clinician who had achieved high levels of inter-rater reliability on all measures ($\kappa \geq 0.9$). Exclusions for all subjects included: IQ<80, substance abuse (within the past three months in the case of BD, lifetime in the case of HV and AR), history of neurological damage or disorder, or pervasive developmental disorder.

BD participants ($n = 19$) met criteria for “narrow phenotype” bipolar disorder including at least one distinct manic or hypomanic episode with elevated or expansive mood (Leibenluft et al., 2003). Seventeen (89.5%) met criteria for BD-I and the remainder met criteria for BD-II. All were euthymic at the time of testing (defined as YMRS ≤ 12 and CDRS ≤ 40 for the past week) and ten (52.6%) were medicated. AR youths ($n = 13$) had a first-degree relative diagnosed with BD (53.8% parent; 46.2% sibling), but had no history of any psychiatric illness themselves, including Attention Deficit Hyperactivity Disorder. HV participants ($n = 21$) had no current or past history of psychiatric illness and no first-degree relatives with a

mood disorder. No participants were related. The groups did not differ significantly on age, gender, or IQ as determined by the Wechsler Abbreviated Scale of Intelligence (Table 1).

Of the 92 individuals scanned for this study, data from 8.7% ($n = 3$ BD, 4 AR, 1 HV) were excluded due to poor task performance (i.e., $< 55\%$ accuracy on go trials), 19.6% ($n = 7$ BD, 3 AR, 8 HV) for excessive movement (> 3 mm or > 3 degrees), 4.3% ($n = 1$ BD, 1 AR, 2 HV) for poor scan quality, 7.6% ($n = 1$ BD, 2 AR, 4 HV) for equipment failure, and 2.2% ($n = 2$ BD) for abnormal brain findings. The final sample ($n = 53$) is presented in the results below. Of these, data from 10 BD and 15 HV participants were reported previously in Leibenluft et al. (2007) and all BD and HV participants were reported in Deveney et al. (2012). Data from all 13 AR youths have not been reported previously and are the focus of this study.

2.2 Stop Signal Task

The stop signal task was modified from Logan and colleagues (1997). Trials consisted of a white fixation cross (500ms) followed by a target stimulus (a white “X” or “O”; 1000ms) presented centrally on a black background. Task instructions were to press the “1” button when an “X” appeared and the “2” button for an “O”. Participants were instructed to respond before the target disappeared from the screen (go trials; 75% of all trials), unless the background of the target changed from black to red (stop trials; 25% of all trials). The first stop signal was presented 250 ms after the target stimulus. Thereafter the interstimulus interval (inhibit delay) between target presentation and stop signal varied on a trial-by-trial basis in response to each subject’s behavior on the previous trial. Successful inhibition increased the inhibit delay interval by 50 ms on the next stop trial (thereby making inhibition more difficult), while unsuccessful inhibition resulted in a 50 ms decrease in inhibit delay on the next stop trial. This ensured accuracy rates of approximately 50% on stop trials, thereby ensuring similar levels of task difficulty across groups and ensuring an adequate number of successful inhibition and unsuccessful trials for analysis.

Trials were randomly presented across a total of 4 runs. Each run consisted of 44 go, 20 stop, and 22 fixation cross trials. Each trial lasted 1500ms and trials were separated by a 750 ms inter-trial interval.

2.3 Scanning acquisition

Participants were scanned in a General Electric Signa 3T magnet at the NIH and viewed stimuli through Avotec Silent Vision Glasses (Stuart, FL) positioned in the head coil above the subject’s eyes. A manual shim procedure and sagittal localization were run prior to obtaining gradient echo planar (EPI) images (23 contiguous 5 mm axial slices/brain volume; parallel to anterior commissure posterior line; single shot gradient echo T2* weighting [matrix 64×64 ; TR = 2000 ms; TE = 40ms; Field of View = 240mm; voxels were $3.75 \times 3.75 \times 5$ mm]). A high-resolution T1 weighted anatomical image was collected following the task according to the following standardized magnetization prepared gradient echo sequence: 180 1 mm sagittal slices; FOV = 256; NEX = 1; TR = 11.4 ms; TE = 4.4 ms; matrix = 256×256 ; TI = 300 ms; bandwidth = 130 Hz/pixel, 33kHz/256 pixels.

2.4 Data Analyses

2.4.1 Behavioral data—Response times (RT) were computed for go trials (GoRT). Accuracy was computed for go trials and stop trials and mean inhibit delay was calculated for each participant on stop trials. Stop signal response time (SSRT) was calculated by subtracting the mean GoRT minus the mean inhibit delay at the point when the participant’s accuracy on stop trials was 50% (Logan et al., 1997). When accuracy rates did not equal 50%, an interpolation algorithm was used to calculate the SSRT by subtracting the mean

inhibit delay from the reaction time at the X%ile of go trials, where X was the participant's accuracy on stop trials. For example, if a participant's stop accuracy was 60%, the RT value at the 60th %ile of GoRT values was used for the SSRT calculation.

Group differences in accuracy, reaction time, mean inhibit delay and SSRT were tested separately using univariate ANOVAs with *Group* (BD, AR, HV) as the between-group factor.

2.4.2 Imaging data—Imaging data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7 (The MathWorks, Natick, MA). Preprocessing included slice timing correction, motion correction, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing (kernel FWHM = 8). The following events were estimated using general linear models: stop correct; go correct (hereafter called “go”), and stop incorrect. Incorrect go trials could not be reliably estimated due to their low number and were therefore excluded from the analysis. A high pass filter (0.0078 Hz) was used. Pair-wise comparisons of event-related response amplitudes were used to develop individual contrast images that were entered into second-level random-effects group analyses.

Our primary analysis focused on three contrasts (stop incorrect-stop correct; stop correct-go; and stop incorrect-go). The stop incorrect vs. stop correct contrast matches for task demands but differs on motor response and thus identifies regions associated with motor response and with successful motor inhibition. Stop correct vs. go matches for successful task performance but differs for motor response and may identify regions associated with successful inhibition. The stop incorrect vs. go contrast matches for motor response and may identify regions associated with unsuccessful inhibition regardless of motor response. Coordinates are reported in MNI space.

Group differences for each contrast were assessed using a factorial ANOVA in SPM8. Next, we identified the following regions of interest: right and left putamen, caudate, nucleus accumbens, ACC, and VLPFC using anatomical templates applied to each participant's data (see Leibenluft et al., 2007 for details). The standard small-volume-correction procedure in SPM8 was used for each region and each contrast to identify clusters whose peak surpassed a significance level corrected for the number of voxels in that anatomical region ($p < .05$). We then extracted an averaged estimated contrast value from each participant for each cluster identified from the group level analysis. These values were then exported into SPSS where post-hoc *t*-tests were conducted to clarify which groups differed in activation in the identified clusters. Pearson correlations between BD youths' neural activation patterns and YMRS and CDRS scores were conducted for neural regions where BD youths differed from HV participants. To investigate the possibility that specific medications may have influenced neural activity on the task, we conducted exploratory analyses in regions where between-group differences were identified in the primary analyses to examine whether BD youths taking certain classes of medications (e.g., atypical antipsychotics) differed from HV youths. The complete analyses and results are included in the supplemental material.

In order to examine whether AR youths differentially recruited brain regions not typically identified in motor inhibition tasks, we conducted an exploratory whole brain analysis using a factorial ANOVA in SPM8. For each of the three contrasts, we used a voxel threshold of $p < .001$ and a Family Wise Error (FWE) correction of $p < .05$ to identify significant clusters.

In addition, in the regions where we observed between-group differences in the primary analysis, we conducted *t* tests comparing AR_{sibling} and HV youths and then AR_{parent} and HV youths to examine whether activation patterns were related to proband relationship.

Because prior studies have examined differences between BD and HV youths in an overlapping sample (Deveney et al., 2012; Leibenluft et al., 2007), we focus on the results involving the unique AR sample. However, we present findings from the BD versus HV groups for completeness and because prior studies used BD youths with a wide range of mood symptoms while the present study only included euthymic youths.

3. Results

3.1 Behavioral Data

Groups did not differ on accuracy or response time on go trials, accuracy on stop trials, inhibit delay, or SSRT (see Table 2).

3.2 Imaging Data: Region-of-interest analyses

Stop correct versus go. No significant group differences were observed on the contrast.

Stop incorrect versus stop correct (Table 3; Figure 1a). The primary analysis identified a 425 voxel cluster in the left putamen where activation differed among groups, $F(2,50) = 11.31$, $p < .01$. Post-hoc tests indicated that mean activation was greater among AR than HV participants ($t(32) = -4.33$, $p < .001$) and tended towards being greater in BD than HV youths ($p < .06$). Activation in this region did not differ between AR and BD youths ($p > .20$).

Stop incorrect versus go (Table 3; Figure 1b). The primary analysis identified group differences in a 555 voxel cluster in the left putamen, $F(2,50) = 10.72$, $p < .02$, and a corresponding 317 voxel cluster in the right putamen $F(2,50) = 9.03$, $p < .04$. Post hoc tests indicated that AR children exhibited greater activation than HV participants in the bilateral putamen (left: $t(32) = 3.95$, $p < .001$; right $t(32) = 2.63$, $p < .02$), and greater activation than BD youths in the right putamen ($t(30) = -2.93$, $p < .01$).

The primary analysis in the right nucleus accumbens identified a cluster (109 voxels) with group activation differences, $F(2,50) = 10.00$, $p < .01$ (Table 1). According to post-hoc tests, BD children exhibited smaller mean activations relative to HV and AR ($t(32) = -2.51$, $p < .02$; $t(30) = -3.27$, $p < .005$, respectively), who did not differ from each other ($p > .40$). BD youths' YMRS and CDRS scores were not significantly correlated with activation in this region ($|r|s < .25$, $ps > .30$).

Results from exploratory analyses did not generally support the hypothesis that atypical antipsychotic or anticonvulsant medications normalized putamen activation in the BD youths (see supplemental material for complete analyses and results).

3.3 Imaging Data: Whole brain analyses

No significant findings survived FWE correction in any of the three contrasts.

3.4 Imaging Data: Impact of Familial At Risk Status

Stratifying the AR group according to whether the child had an affected parent or sibling indicated that the primary findings reported above were present in both AR groups. Specifically, both AR_{parent} and AR_{youth} exhibited greater left putamen activation than HV youths in the primary stop incorrect vs. stop correct contrast (AR_{parent}: $t(26) = -4.32$, $p < .001$; AR_{sibling}: $t(25) = -2.41$, $p < .03$). Both AR groups also exhibited more activation than HV youths in the stop incorrect vs. go contrast in the left putamen (AR_{parent}: $t(26) = 2.89$, $p < .01$; AR_{sibling}: $t(25) = 2.40$, $p < .03$) with similar trends in the right putamen ($ps < .07$).

4. Discussion

We examined the neural circuitry mediating motor inhibition among asymptomatic children and adolescents at risk for BD compared with euthymic youths with BD and healthy volunteers. This analysis helps to identify neural abnormalities in pediatric BD unconfounded by prior episodes of mania and depression, current mood state, comorbid diagnoses, and prior treatment. Although behavioral performance did not differ among groups, differences in neural activation emerged. Youths at familial risk for BD exhibited increased activation during unsuccessful inhibition (relative to correctly inhibited and go trials) that distinguished them from HV in the left putamen and from the HV and BD youths in the right putamen. Euthymic youths with BD differed from the other groups in having reduced activation of the right nucleus accumbens during unsuccessful inhibition relative to correct go responses. No group differences were found in the VLPFC or the ACC.

Our finding of striatal dysfunction in the AR sample extends previous studies in youths with BD (Adleman et al., 2011, Blumberg et al., 2003; Chang et al., 2004; Dickstein et al., 2007; Leibenluft et al., 2007) and could suggest that dysfunction in the putamen is associated, not only with affected status, but also with risk for the illness. In that regard, our data also extend studies in unaffected adult relatives of adults with BD that found behavioral deficits in the relatives on striatally-mediated cognitive control tasks such as the Stroop and Wisconsin Card Sort Tasks (Arts et al., 2008; Bora et al., 2009). Our findings are particularly notable because none of the at-risk participants met criteria for psychiatric illness, and all were medication naïve. Together, these findings suggest that striatal dysfunction is associated with risk for BD. In contrast, we did not observe aberrant activation of the ACC or VLPFC in the AR sample. Future studies using larger samples would clarify whether AR youths exhibit dysfunction in these regions.

However, interpretation of these findings is complicated by the fact that the AR youths' neural activation differed from both HV and BD youths in a region where BD and HV groups did not differ from each other. Such findings generally do not conform to endophenotype criteria and complicate interpretations about the possible neural markers of BD (Gottesman and Gould, 2003). One possibility is that hyperactivation of striatal regions during unsuccessful inhibition is a marker of resilience in youths at familial risk for BD. Alternatively, increased striatal recruitment during unsuccessful inhibition may represent a marker of dysfunction that occurs prior to the onset of BD illness and that neural activation patterns change over time – perhaps as a consequence of treatment with psychotropic medications. Longitudinal studies in AR youths, followed as they mature to develop BD or remain resilient, would disambiguate these hypotheses.

These findings are also complicated by the lack of group differences on the behavioral measures of motor inhibition. The observed neural differences between AR and HV youths were not associated with between-group differences in the amount of time it takes each participant to stop a motor response, as measured by the SSRT. It is always difficult to interpret null findings, and the relatively small number of AR youths in the sample makes us particularly reticent to conclude that AR youths are unimpaired on motor inhibition tasks. In addition, there is no clear consensus in the literature about how to interpret neural activity differences in the absence of behavioral differences (e.g., Wilkinson & Halligan, 2004). However, there are several possible explanations for the discrepancy between the neuroimaging and behavioral findings. First, fMRI may be more sensitive to deficits among BD and AR youths than are behavioral measures. Indeed, neuroimaging studies frequently document intact behavioral performance but differing neural activation patterns between BD youths and healthy children (Finger et al., 2008; Pliszka et al., 2006; Singh et al., 2010). Second, the unique nature of the scanning environment may reduce behavioral differences

between diagnostic groups. For example, the limited visual stimuli present in the scanner might facilitate BD and AR youths' attention to the task and improve performance. A third possibility is that the observed neural differences reflect inefficiency or overcompensation by AR youths in order to achieve the same behavioral performance as healthy comparison children. Fourth, our lack of behavioral findings is not unexpected, since studies in the literature are inconsistent as to whether motor inhibition deficits are detected in youth with BD. Although several studies have observed motor inhibition deficits in behavioral tasks in BD and AR youths (Passarotti et al., 2010; Peluso et al., 2007; Swan et al., 2001, 2003, 2004), other studies have failed to do so (e.g., Cerullo et al., 2009; Leibenluft et al., 2007; McClure et al., 2005; Singh et al., 2010). Finally, the striatal deficits among AR youths may not be substantial enough to impact performance on this behavioral task but might make them more likely to experience problems inhibiting motor responses in other contexts. For example, recent research suggests that the inclusion of emotional stimuli in cognitive tasks impacts the behavioral and neural performance of BD youths (e.g., Passarotti et al., 2010b). Future research could examine whether the striatal abnormalities observed in the present study exist and impair behavioral performance of AR youths on a motor inhibition task that incorporates emotional stimuli. Future studies would also benefit from the use of connectivity analyses to examine whether the relationships between neural regions that mediate motor inhibition differ between participant groups and may confer risk for BD. The lack of such analyses is a limitation of the present study.

In addition, our results differ somewhat from our prior studies using the same task with overlapping populations. In that study, BD patients exhibited decreased activation during failed inhibition trials across the striatum and in the VLPFC (Leibenluft et al., 2007), whereas in the present study this was significant only in the right nucleus accumbens. We cannot rule out the contribution of methodological differences between the two studies including the use of different analytic software (SPM99 vs. SPM8) and the use of peak voxel activation in the earlier study versus mean activation across the cluster in the present study. However, we believe the most likely explanation for our failure to replicate prior findings is the reduced statistical power associated with a) using euthymic BD youths only and b) including three separate participant groups in the present study.

The main limitation of our study is small sample size, particularly in the AR group. Medication-naïve, illness-free youths at risk for BD are difficult to recruit, hence our sample of only thirteen AR subjects and the scarcity of prior research with this population. Due to equipment changes at the NIH, we were unable to recruit additional participants without introducing an additional confounding variable of scanner change between groups. Our AR sample included both youth who were at risk for BD due to a parent with the illness and those at risk because of an affected sibling. Considering these groups together may have limited our ability to detect differences in brain activity between the AR youths and the BD and HV populations. However, the significant differences observed between the entire AR sample and the HV youths were unlikely to be related to the nature of an individual's familial risk because our post-hoc analyses indicated that each of the AR sub-groups differed from healthy subjects, at least at a trend level. These conclusions are tentative given the small number of participants in each AR group; we are unaware of any literature that examines whether neural circuitry differs between youths with different types of familial risk for BD. Future research with a larger sample size may clarify the relative contributions of risk for BD by virtue of having a parent or a sibling with the illness.

4.1 Conclusions

This investigation of the neural correlates of motor response inhibition in euthymic youths with BD, unaffected youths with a first degree relative with BD, and healthy comparison children revealed between-group differences in putamen activation during unsuccessful

inhibition. Specifically, children at risk for BD recruited the putamen to a greater degree than the healthy comparison children, while BD youths did not differ from either participant group. These findings, which require replication and extension, suggest that familial risk for BD may be associated with striatal dysfunction. Future research with children at familial risk for BD should focus on clinical, neuropsychological, neuroimaging and genetic neuroimaging studies of impulsivity and motor inhibition and may wish to explore the role of emotional stimuli on these processes. Ultimately, as noted above, cross-sectional studies should be complemented by longitudinal studies examining whether at-risk youths with striatal dysfunction, impaired motor inhibition and/or impulsivity are at higher risk to develop the illness than at-risk youths without such biomarkers or clinical findings.

Highlights

- Youths at-risk for BD showed intact motor inhibition measured behaviorally
- Youths at-risk for BD had hyperactivation of the putamen during failed inhibition
- BD youths showed hypoactivation of the nucleus accumbens during failed inhibition

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health. We thank the children and families for their participation which made this research possible. We also thank the staff of the Emotion and Development Branch at NIMH.

Abbreviations

BD	bipolar disorder
AR	at-risk
HV	healthy volunteer
VLPFC	ventrolateral prefrontal cortex
ACC	anterior cingulate cortex

References

- Adleman NE, Kayser R, Dickstein DP, Blair RJR, Pine DS, Leibenluft E. Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2011
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders fourth-TR edition*. Washington DC: American Psychiatric Association; 2000.
- Aron AR. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol Psychiatry*. 2011; 69:e55–e68. [PubMed: 20932513]
- Arts B, Jabben N, Krabbendam L, van Os J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med*. 2008; 38:771–785. [PubMed: 17922938]
- Blumberg HP, Martin A, Kaufman J, Leung HC, Skudlarski P, Lacadie C, Fulbright RK, Gore JC, Charney DS, Krystal JH, Peterson BS. Frontostriatal abnormalities in adolescents with bipolar

- disorder: preliminary observations from functional MRI. *Am J Psychiatry*. 2003; 160:1345–1347. [PubMed: 12832254]
- Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affective Disord*. 2009; 113:1–20.
- Brotman MA, Guyer AE, Lawson ES, Horsey SE, Rich BA, Dickstein DP, Pine DS, Leibenluft E. Facial emotion labeling deficits in children and adolescents at risk for bipolar disorder. *Am J Psychiatry*. 2008; 165:385–389. [PubMed: 18245180]
- Brotman MA, Rooney MH, Skup M, Pine DS, Leibenluft E. Increased intrasubject variability in response time in youths with bipolar disorder and at-risk family members. *J Am Acad Child Adolesc Psychiatry*. 2008; 48:628–635. [PubMed: 19454918]
- Brotman MA, Skup M, Rich BA, Blair KS, Pine DS, Blair JR, Leibenluft E. Risk for bipolar disorder is associated with face-processing deficits across emotions. *J Am Acad Child Adolesc Psychiatry*. 2008; 47:1455–1461. [PubMed: 19034190]
- Cerullo MA, Adler CM, Lamy M, Eliassen JC, Fleck DE, Strakowski SM, DelBello MP. Differential brain activation during response inhibition in bipolar and attention-deficit hyperactivity disorders. *Early Interv Psychiatry*. 2009; 3:189–197. [PubMed: 22640382]
- Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev*. 2009; 33:631–646. [PubMed: 18835296]
- Chang K, Adelman NE, Dienes K, Simeonova DI, Menon V, Reiss A. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. *Arch Gen Psychiatry*. 2004; 61:781–792. [PubMed: 15289277]
- Deveney CM, Connolly ME, Jenkins SE, Kim P, Fromm SJ, Brotman MA, Pine DS, Leibenluft E. Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biol. Psychology*. 2012; 89:148–155.
- Dickstein DP, Rich BA, Roberson-Nay R, Berghorst L, Vinton D, Pine DS, Leibenluft E. Neural activation during encoding of emotional faces in pediatric bipolar disorder. *Bipolar Disord*. 2007; 9:679–692. [PubMed: 17988357]
- Diwadkar VA, Goradia D, Hosanagar A, Mermon D, Montrose DM, Birmaher B, Axelson D, Rajarathinam R, Haddad L, Amirsadri A, Zajac-Benitez C, Rajan U, Keshavan MS. Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35:1349–1354. [PubMed: 21549798]
- Doyle AE, Wozniak J, Wilens TE, Henin A, Seidman LJ, Petty C, Fried R, Gross LM, Faraone SV, Biederman J. Neurocognitive impairment in unaffected siblings of youth with bipolar disorder. *Psychol Med*. 2009; 39:1253–1263. [PubMed: 19079809]
- Finger EC, Marsh AA, Mitchell DG, Reid ME, Sims C, Budhani S, Kosson DS, Chen G, Towbin KE, Leibenluft E, Pine DS, Blair RJR. Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Arch Gen Psychiatry*. 2008; 65:586–594. [PubMed: 18458210]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for the DSM-IV TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute, Biometrics Research; 2002.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Kaufmann J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997; 36:980–988. [PubMed: 9204677]
- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003; 160:430–437. [PubMed: 12611821]

- Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, Joshi P, Robb A, Schachar RJ, Dickstein DP, McClure EB, Pine DS. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. *Am J Psychiatry*. 2007; 164:52–60. [PubMed: 17202544]
- Logan GD, Schachar RJ, Tannock R. Impulsivity and inhibitory control. *Psychol Sci*. 1997; 8:60–64.
- McClure EB, Treland JE, Snow J, Schmajuk M, Dickstein DP, Towbin KE, Charney DS, Pine DS, Leibenluft E. Deficits in social cognition and response flexibility in pediatric bipolar disorder. *Am J Psychiatry*. 2005; 162:1644–1651. [PubMed: 16135623]
- Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry*. 1994; 51:849–859. [PubMed: 7944874]
- Padmala S, Pessoa L. Interactions between cognition and motivation during response inhibition. *Neuropsychologia*. 2010; 48:558–565. [PubMed: 19879281]
- Passarotti AM, Sweeney JA, Pavuluri MN. Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. *Psychiatry Res: Neuroimaging*. 2010a; 181:36–43.
- Passarotti AM, Sweeney JA, Pavuluri MN. Emotion processing influences working memory circuits in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2010b; 49:1064–1080. [PubMed: 20855051]
- Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. Enhanced prefrontal function with pharmacotherapy on a response inhibition task in adolescent bipolar disorder. *J Clin Psychiatry*. 2010; 71:1526–1534. [PubMed: 20816040]
- Peluso MA, Hatch JP, Glahn DC, Monkul ES, Sanches M, Najt P, Bowden CL, Barratt ES, Soares JC. Trait impulsivity in patients with mood disorders. *J Affective Disord*. 2007; 100:227–231.
- Pliszka SR, Glahn DC, Semrud-Clikeman M, Franklin C, Perez R, Xiong J, Liotti M. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *Am J Psychiatry*. 2006; 163:1052–1060. [PubMed: 16741206]
- Poznanski EO, Cook SC, Carroll BJ. A depression rating scale for children. *Pediatrics*. 1979; 64:442–450. [PubMed: 492809]
- Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 2003; 20:351–358. [PubMed: 14527595]
- Swann AC, Anderson JC, Dougherty DM, Moeller FG. Measurement of inter-episode impulsivity in bipolar disorder. *Psychiatry Res*. 2001; 101:195–197. [PubMed: 11286822]
- Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disord*. 2004; 6:204–212. [PubMed: 15117399]
- Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG. Impulsivity and phase of illness in bipolar disorder. *J Affective Disord*. 2003; 73:105–111.
- Singh MK, Chang KD, Mazaika P, Garrett A, Adleman N, Kelley R, Howe M, Reiss A. Neural correlates of response inhibition in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol*. 2010; 20:15–24.
- Singh MK, DelBello MP, Fleck DE, Shear PK, Strakowski SM. Inhibition and attention in adolescents with nonmanic mood disorders and a high risk for developing mania. *J Clin Exper Neuropsychol*. 2009; 31:1–7. [PubMed: 18608697]
- Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu H, Joyce PR, Karam EG, Lee C, Lellouch J, Lépine J, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh E. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996; 276:293–299. [PubMed: 8656541]
- Wilkinson D, Halligan P. The relevance of behavioural measures for functional-imaging studies of cognition. *Nature Rev Neurosci*. 2004; 5:67–73. [PubMed: 14708005]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry*. 1978; 133:429–435. [PubMed: 728692]

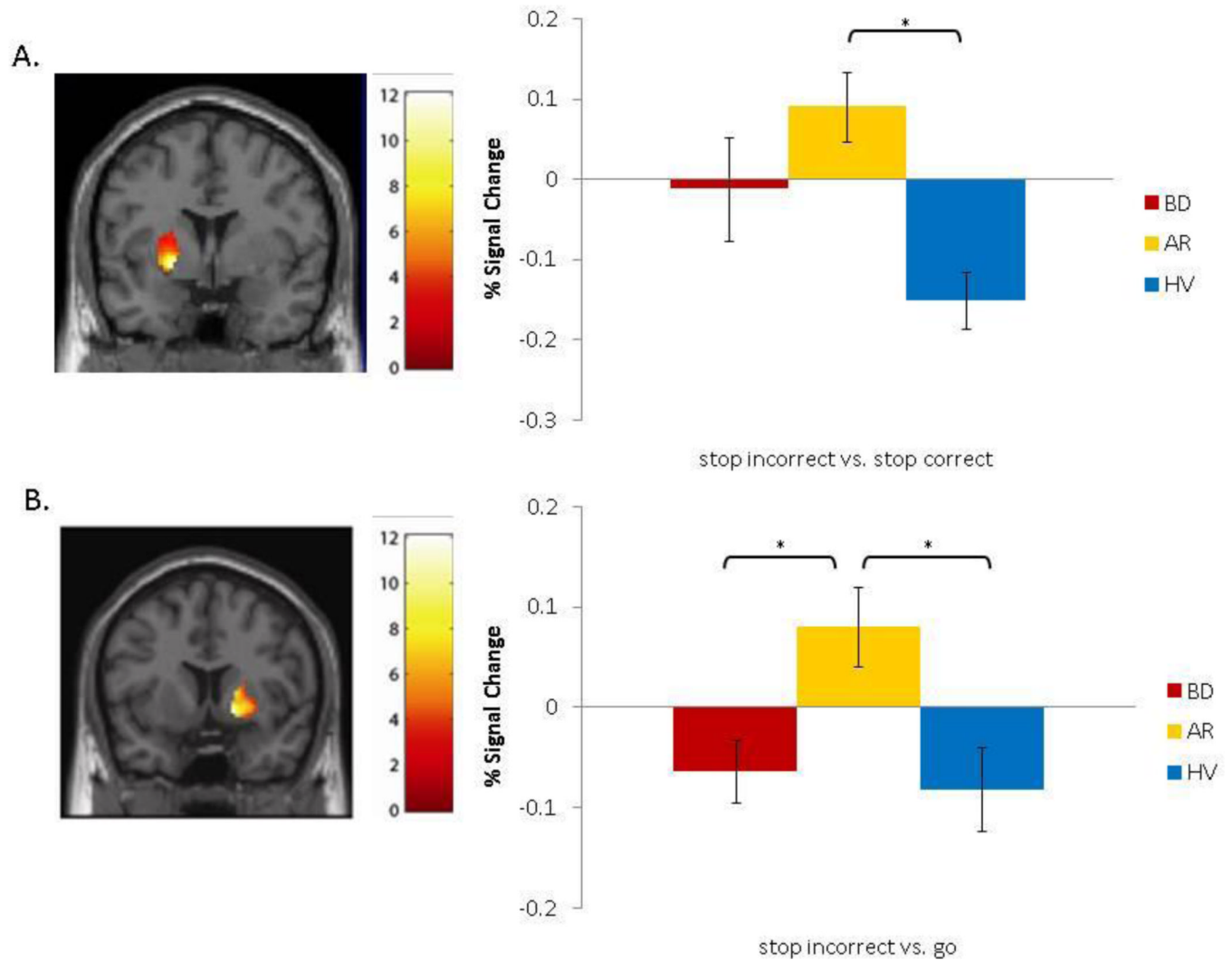


Figure 1.

Panel A: Activation on stop incorrect vs. stop correct trials of patients with bipolar disorder, at-risk youths, and healthy volunteers in the left putamen (MNI coordinates $x = -22$, $y = 2$, $z = -4$). Panel B: Activation on stop incorrect versus go trials of patients with bipolar disorder, at risk youths, and healthy volunteers in the right putamen (MNI coordinates $x = 16$, $y = 8$, $z = -4$). BD = bipolar disorder; AR = at-risk; HV = healthy volunteers. * = $p < .05$

Table 1
Demographic and clinical characteristics of patients, at-risk youths, and healthy volunteers

Characteristic	Patients with BD (N= 19)		At-Risk Youths (N=13)		Healthy Volunteers (N = 21)		<i>p</i>
	Mean (SD)		Mean (SD)		Mean (SD)	<i>F</i> (df) [†]	
Age (years)	14.76 (2.9)		13.46 (1.8)		13.78 (2.0)	1.43 (2,52)	> .20
WASI two-scale IQ	111.16 (15.6)		109.00 (13.6)		113.67 (14.2)	0.43 (2,52)	> .65
YMRS	6.05 (3.7)		---		---	---	---
CDRS [†]	22.42 (5.7)		---		---	---	---
Number of Medications	1.79 (1.9)		---		---	---	---
Number of Comorbid Diagnoses	1.89 (1.6)		---		---	---	---
<hr/>							
	N (%)		N (%)		N (%)	χ^2 (df)	<i>p</i>
Male	7 (36.8)		6 (46.2)		13 (61.9)	2.57 (2)	> .25
BPI	17 (89.5)		---		---	---	---
BPII	2 (10.5)		---		---	---	---
Comorbid Diagnoses							
ADHD	9 (47.4)		---		---	---	---
Anxiety	7 (36.8)		---		---	---	---
ODD or CD	5 (26.3)		---		---	---	---
Medication							
Unmedicated	9 (47.4)		13 (100)		---	---	---
Atypical Antipsychotic	8 (42.1)		---		---	---	---
Lithium	5 (26.3)		---		---	---	---
Antiepileptic	8 (42.1)		---		---	---	---
Antidepressant	4 (21.1)		---		---	---	---
Stimulants	4 (21.1)		---		---	---	---

Note: BD = Bipolar Disorder; WASI = Weschler Abbreviated Scale of Intelligence (two-scale IQ); YMRS = Young Mania Rating Scale; CDRS = Children's Depression Rating Scale; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder.

[†] Statistics for demographic variables reflect the comparison between all three participant groups.

Table 2

Behavioral performance of patients with BD, at-risk youth, and healthy volunteers

Characteristic	Patients with BD (N = 19)		At-Risk Youths (N = 13)		Healthy Volunteers (N = 21)		p >
	Mean (SD)		Mean (SD)		Mean (SD)		
Percent Accuracy Go Trials	86.05 (9.80)		81.64 (10.80)		83.92 (11.40)		0.50
Percent Accuracy Stop Trials	51.39 (7.17)		52.74 (6.92)		53.36 (10.80)		0.70
Mean Go Response Time	677.21 (80.61)		700.38 (101.75)		696.81 (109.35)		0.70
Stop Signal Response Time	204.67 (37.26)		211.28 (38.21)		196.52 (40.93)		0.50
Inhibit Delay	473.41 (104.40)		498.14 (113.45)		503.70 (123.50)		0.60

note: BD = Bipolar Disorder

Significant between-group differences in activation on the incorrect vs. stop correct and stop incorrect vs. go contrasts and the post-hoc analyses of stop correct vs. fixation, stop incorrect vs. fixation, and go vs. fixation contrasts.

Table 3

Area of Activation	Side	cluster size [†]	MNI coordinates			F (2,50)	p <	Between-group differences
			x	y	z			
<i>stop incorrect vs. stop correct</i>								
Putamen	L	425	-22	2	-4	11.31	.01	AR>HV ^{***} ; BD>HV [*]
<i>stop incorrect vs. go</i>								
Putamen	L	555	-32	-10	2	10.72	.02	AR>HV ^{***} ; AR>BD ^{**}
Putamen	R	317	16	8	-4	9.03	.04	AR>HV ^{**} ; AR>BD ^{***}
Nucleus Accumbens	R	109	14	6	-6	10.00	.01	HV>BD ^{**} ; AR>BD ^{***}

* $p < .10$,
** $p < .05$,
*** $p < .01$

BD = bipolar disorder, AR = youths at risk for BD; HV = healthy volunteer.
x,y, and z coordinates refer to the voxel with maximum signal intensity

[†] determined using a significance threshold of $p < .05$ and corrected for the number of voxels in each region