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Behavioral and Neural Sustained Attention Deficits in Bipolar Disorder and Familial Risk for Bipolar Disorder

David Pagliaccio, Ph.D.^{a,*}, Jillian Lee Wiggins, Ph.D.^{b,c}, Nancy E. Adleman, Ph.D.^d, Elizabeth Harkins, B.A.^e, Alexa Curhan, B.A.^a, Kenneth E. Towbin, M.D.^a, Melissa A. Brotman, Ph.D.^a, Daniel S. Pine, M.D.^a, and Ellen Leibenluft, M.D.^a

^aEmotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

^bDepartment of Psychology, San Diego State University, San Diego, CA 92182, USA

^cSan Diego State University/ University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA 92120

^dDepartment of Psychology, The Catholic University of America, Washington, DC 20064, USA

^eSchool of Nursing, Johns Hopkins University, Baltimore, MD 21205, USA

Abstract

Background—Few neuroimaging studies compare individuals affected with bipolar disorder (BP), at high familial risk for BP, and at low risk to identify endophenotypes for BP. None have examined variability in attention, despite promising behavioral work in this area. We used functional magnetic resonance imaging (fMRI) methods uniquely powered to compare the neural correlates of attention variability in these three groups.

Methods—The current study examined 106 8–25-year-olds who completed an fMRI attention task: 24 with BP, 29 at-risk based on a first-degree relative with BP, and 53 healthy, low-risk individuals. Group differences in intra-subject variability in reaction time were examined and a sophisticated fMRI analytic approach was used to quantify precisely trial-wise associations between reaction time and brain activity. The latter has not been examined previously in BP or risk for BP.

Results—Relative to healthy individuals, those with BP or at-risk for BP exhibited increased reaction time variability ($F(2,102)=4.26$, $p=.02$, $\eta_p^2=0.08$). Importantly, we identified blunted relationships between trial-wise variation in reaction time and brain activity in the inferior and middle frontal gyri, precuneus, cingulate cortex, caudate, and postcentral gyrus (all regions: $p<.001$, $\eta_p^2>0.06$) in both at-risk and BP individuals compared to healthy, low-risk individuals. This

*Corresponding author: David Pagliaccio, Emotion and Development Branch, National Institute of Mental Health, Building 15K, MSC 2670, Bethesda, MD 20892, pagliaccioid@mail.nih.gov; avid.pagliaccio@gmail.com.

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blunting partially mediated group differences in reaction time variability ($\beta=0.010$, 95% Confidence Interval=[0.002–0.020], Sobel $Z=2.08$, $p=.038$).

Conclusions—Blunting in key frontal, cingulate, and striatal areas was evident in unaffected, at-risk individuals and in euthymic BP patients. Elucidating such novel neural endophenotypes can facilitate new approaches to BP prediction, diagnosis, and prevention.

Keywords

Bipolar Disorder; Risk; fMRI; Attention; Reaction Time; Intra-Individual Variability; Inferior Frontal Gyrus

Introduction

Intra-subject variability in reaction time (ISVRT) represents a promising *behavioral* endophenotype (1) for bipolar disorder (BP). ISVRT is a heritable index of sustained-attention deficits (2) in both manic and euthymic adults with BP (3). Increased ISVRT generally arises from having frequent long reaction-time (RT) trials (4), likely due to momentary attentional lapses. Identifying endophenotypes, such as increased ISVRT, can facilitate improved BP prediction, diagnosis, and prevention. While most developmental psychopathology studies examine ISVRT behavior in ADHD (5–7), the few studies on youth with or at-risk (AR) for BP find increased ISVRT, compared to healthy, low-risk youths (8, 9). The current study extends this prior behavioral work through brain imaging.

No prior studies have mapped the *neural* correlates of ISVRT in BP. In fact, few functional magnetic resonance imaging (fMRI) studies have tested any psychological process as a potential neural endophenotype by comparing both BP and AR individuals to low-risk individuals. Moreover, the few such studies that do examine these three groups focus predominantly on emotion processing, despite meta-analytic work indicating robust behavioral deficits in sustained attention (10). Finally, only half of the fMRI studies on risk for BP examine youth or young adults (11–16); the other half examines middle-aged adults (17–23). More studies in youth are needed, particularly as middle-aged relatives of BP patients are beyond the typical age of BP onset (24). Thus, studies in older age groups likely include many resilient rather than at-risk individuals.

While no studies have mapped the neural correlates of ISVRT in BP, studies in healthy individuals set the stage for such work. These studies find that ISVRT correlates with engagement of middle frontal gyrus (MFG), caudate, and postcentral gyrus (25, 26). Further work in healthy adults has capitalized on advanced MRI methods to more directly assess the neural mechanisms of ISVRT by precisely quantifying the relationship between *trial-by-trial* variation in RT and bloodoxygen- level dependent (BOLD) signal. Studies using these methods identify robust “RT-BOLD relationships” during executive function tasks in key frontal and parietal regions involved in cognitive control and attention (27–29). Of note, this unique trial-by-trial analysis captures particularly strong brain-behavior relationships that would not be evident using traditional fMRI analyses, which average across all trials in a condition. Specifically, Weissman et al. (2006) note trial-by-trial associations between attentional lapses and 1) pre-stimulus dips in anterior cingulate cortex (ACC), inferior

frontal gyrus (IFG), and MFG activity; 2) increased compensatory activity in frontal, parietal, and subcortical regions; and 3) less task-related deactivation of default mode network regions. This trial-by-trial method also has been used successfully to associate weakened RT-BOLD associations with weakened attention control in sleep deprivation and (30, 31) and in youth vs. adults (32). The current study builds on this uniquely powerful research strategy to examine BP.

Examining youth and young adults with or at-risk for BP, we test two hypothesis addressing attentional variability as a potential BP endophenotype. First, we test the hypothesis that, relative to healthy, low-risk individuals, BP and AR individuals both would show increased ISVRT on a task not used previously in these populations. Second, we use brain imaging to examine neural correlates of this potential behavioral endophenotype, utilizing the analytic method described above to quantify precisely trial-wise relationships between brain activity and RT. Specifically, on trials with relatively long RT, we hypothesized that AR and BP individuals would show altered frontal activity prior to stimulus presentation; deficits in compensatory fronto-cingulate activity; and deficits in task-related deactivation of default mode network regions. Applying these methods in an understudied population could identify a previously-unrecognized neural endophenotype while explicating attentional deficits in BP (10).

Methods and Materials

Participants

Participants enrolled in an Institutional Review Board-approved protocol at the National Institute of Mental Health in Bethesda, MD. Minors (<18 years) and their guardians provided written informed assent and consent, respectively. Adult participants provided written consent. We examined three biologically unrelated groups: individuals with BP, individuals at-risk for BP based on having a first-degree relative with the disorder, and low-risk healthy volunteers (HV) without a personal history of any psychiatric diagnoses or a first-degree relative with BP.

Children's psychiatric diagnoses were assessed using parent- and child-report on the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (KSADS) (33). Adult participants were assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (34). Comorbid diagnoses were assigned based on symptoms present during euthymia. At-risk individuals had a full sibling and/or parent with DSM-IV-TR bipolar I or II disorder. Parent diagnoses of BP were confirmed using the SCID or the Diagnostic Interview for Genetic Studies (35) and sibling diagnoses of BP were confirmed using the KSADS. No sibling pairs were included in this analysis; when multiple siblings were enrolled, we selected only one sibling per family who would maximize the number of BP and AR individuals and minimize group differences in age and sex distributions.

To assess mood near the time of scanning, clinicians interviewed AR and BP children/adolescents (<18 years old; N=25 AR, N=10 BP) and their guardians separately, or AR and BP participants over 18 years old (N=4 AR, N=14 BP), within one week of scanning using

several measures. Depressive symptoms were assessed in children/adolescents using the Children's Depression Rating Scale (CDRS) (36) and in adults using the Structured Interview Guide for the Hamilton Depression Rating Scale - Seasonal Affective Disorders version (SIGH-SAD) (37). Anxiety symptoms were assessed in children/adolescents using the Pediatric Anxiety Rating Scale (PARS) (38). General functioning was assessed in children/adolescents using the Children's Global Assessment Scale (CGAS) (39) and in adults using the Global Assessment of Function (GAF) (40). The Young Mania Rating Scale (YMRS) (41) was used to assess mania symptoms in all AR and BP participants.

Participants were excluded for pervasive developmental disorders, schizophrenia, IQ lower than 70 on the Wechsler Abbreviated Scale of Intelligence (42), substance abuse within the past 2 months, significant medical illness, head trauma, neurological disorder, contraindications to MRI, or treatment with long-acting stimulants. Participants taking short-acting stimulant medications (N=5 BP) withheld their stimulants for 48 hours before scanning. At-risk individuals were not excluded for mood pathology (other than BP or Disruptive Mood Dysregulation Disorder) to avoid recruiting a particularly resilient group (12, 43). Sixteen of the AR individuals had no lifetime diagnoses (Table 1).

Of the 121 individuals (8–25 years old) who completed the fMRI scan successfully, data were excluded from one who did not withhold stimulants, five for task accuracy below 70%, and nine for excessive head motion (see Imaging Analysis). Exclusion (4 BP, 3 AR, 8 HV) did not differ by group ($\chi^2(2)=0.39$, $p=.82$). The final sample included 106 participants: 53 healthy volunteers (9.5–24.6 years old), 29 at-risk individuals (8.9–20.6 years old), and 24 individuals with BP (12.8–24.6 years old).

In-Scanner Behavioral Paradigm

Participants performed a modified global-local selective attention task (27). The task included four stimuli (Figure S1) that appeared with equal frequency. Each stimulus was a large letter ("H" or "S") made up of smaller letters ("Hs" or "Ss"). Half of the stimuli were congruent (e.g., large H comprised of small Hs) while the other half were incongruent (e.g., large S comprised of small Hs). All stimuli were centered on a red fixation point. Each stimulus appeared for 200ms followed by 2300ms of fixation.

During six alternating runs (each with 96 trials: 48 congruent and 48 incongruent), participants were asked to identify, by button-press, either the large global letter or the small local letters. Stimulus presentation and jitter orders were optimized and pseudo-randomized using AFNI's `make_random_timing.py` program. Inter-stimulus intervals were jittered in TR increments (1250ms), ranging from 2.5s to 16.25s (mean=3.98s).

Behavioral Data Analysis

Analyses examined mean RT, standard deviation of RT, and ISVRT, excluding trials with no response or an RT <300ms after stimulus onset. The behavioral measure of interest, ISVRT, was calculated as the coefficient of variation of reaction time (CV-RT; SD/mean RT). Using CV-RT mitigates issues of correlation between mean and standard deviation of RT (44). See Table S1 for a summary of the behavioral data by group and condition. A repeated measures ANCOVA predicting ISVRT was conducted using SPSS v22 (45) with condition (congruent

vs. incongruent) as a within-subject factor, group (HV, AR, BP) as a between-subjects factor, and age at scan (years) as a continuous covariate (due to group differences in age; see Results). Post-hoc Fisher's Least Significant Difference (LSD) tests were used to examine group differences.

Imaging Acquisition and Analysis

Neuroimaging data were collected using a 3T General Electric Signa scanner and 32-channel head coil. Structural images were preprocessed using FreeSurfer v5.3.0 (46). Functional data were analyzed using Analysis of Functional NeuroImages (47) (AFNI; <http://afni.nimh.nih.gov/afni/>) with standard preprocessing (for acquisition and processing details, see Supplemental Information). This work utilized the computational resources of the NIH HPC Biowulf cluster (<http://hpc.nih.gov>).

To control for head motion, we excluded pairs of successive TRs where the sum head displacement between them exceeded 1mm and TRs where more than 10% of voxels were outliers. Participants were excluded if the average motion per TR after censoring exceeded 0.25mm or if more than 15% of TRs were censored for motion/outliers. The proportion of TRs censored did not differ by group ($F(2,104)=1.04$, $p=.36$, $\eta_p^2=0.02$).

Mean standardized reaction time (MSRT) was calculated to mean-center RTs. Specifically, for each trial, we subtracted the participant's mean RT for that trial type (congruent or incongruent) in the same run from that trial's RT (27). A lower MSRT indicated a faster RT relative to one's run- and condition-wise mean RT, while higher MSRT indicated slower relative RT.

To quantify precisely the shape/timing of the RT-BOLD relationship, we did not assume a BOLD response shape. Instead, we analyzed the fMRI data using a linear regression model with an estimated shape method (48) i.e., a finite impulse response model. Each trial was modeled with 13 basis functions (tent function), each of which spanned 1 TR (1250ms). Thus, each trial was modeled with a 16.25s (13 TRs) window starting 2.5s before stimulus onset. Third-order Legendre polynomials modeling baseline drift and 6 head motion parameters were included in each participant's model to control for potential confounding effects.

Each participant's model included regressors (each with 13 tents/TRs) for congruent, incongruent, and error trials. This allowed us to examine average stimulus-locked BOLD response (results in Supplemental information), as in standard fMRI analyses. Additionally, each model included regressors for modulation by MSRT on congruent and incongruent trials. Including amplitude modulation by trial-wise MSRT allowed us to examine trial-by-trial associations between variation in BOLD response and variation in RT (27). Regression coefficients for the amplitude modulation effects indicate differences in percent signal change per second increase above one's mean RT, indexing the strength of the RT-BOLD association.

Examining Group Differences in Brain Activity

The main analysis used multivariate models (49) (3dMVM in AFNI) to examine group differences in RT-BOLD relationships. The models included group (HV, AR, BP) as a three-level between-subjects factor, within-subject factors for condition (congruent, incongruent) and timepoint (TR/'tent'), and covaried for age at scan. Since our goal was to identify group differences, we examined only the group $\times$ timepoint and group $\times$ condition $\times$ timepoint contrasts. As this task has not been examined in BP or AR individuals previously, we examined whether group differences were apparent across conditions or were specific to one condition. Group differences in average BOLD are presented in the Supplemental Information (Table S3, Figures S2–3), to facilitate comparison to standard fMRI analyses.

Monte Carlo simulations (3dClustSim; see Supplemental Information) were used to correct for multiple comparisons. To obtain a whole-brain family-wise error correction of $p < .01$, all results were thresholded at a voxel-wise $p < .0002$ and a cluster extent of 31 voxels. Average activity was extracted from each cluster for post-hoc analyses and visualization. Greenhouse-Geisser adjustment corrected for violations of sphericity. Pairwise post-hoc group t-tests were run at each timepoint to parse group differences.

Post-hoc Control Analyses

While all primary analyses covaried for age, we also examined group differences in ISVRT and RT-BOLD in a subsample of 77 11–22-year-old individuals where age did not differ significantly by group. Additionally, we ran four additional sets of post-hoc ANCOVAs to test for effects of potential confounds, including ADHD, MDD in AR individuals, current mood, and medication usage. See Supplemental Information for details.

Results

Demographics and Diagnostics

The three groups did not differ based on sex or IQ (Table 1). AR individuals were younger than HV (mean difference=3.84, $p < .001$) and BP individuals (mean difference=4.22, $p < .001$). Thus, age was covaried in all analyses, and secondary analyses examined a sub-sample that did not differ on age. As expected, compared to AR individuals, BP individuals had lower general functioning (CGAS/GAF) and increased mania symptomology (YMRS), as well as higher rates of ADHD, anxiety disorders, and medication use. The groups did not differ on ratings of anxiety (PARS) or depression (CDRS, SIGH-SAD). Of the 24 BP patients, 15 met criteria for BP-I and 9 met criteria for BP-II. These BP subgroups did not differ in current functioning, current mood, ISVRT, or RT-BOLD (Supplemental Information).

Behavioral Effects

Using a repeated measures ANCOVA, we found an effect of group predicting ISVRT ($F(2,102)=4.26$, $p=.02$, $\eta_p^2=0.08$; Figure 1), but no effects of age, condition, or group $\times$ condition (all $ps > .14$). Post-hoc LSD tests indicated greater ISVRT among BP (mean difference=0.03, $p=.02$, 95% CI=0.01–0.06) and AR individuals (mean difference=0.03, $p=.03$, 95% CI=0.003–0.05) vs. HV individuals, with no significant differences between BP and

AR individuals. Table S2 presents ANCOVA effects on ISVRT, accuracy, mean RT, and SD of RT in the full sample and age-restricted subsample.

RT-BOLD Effects

Nine regions showed group $\times$ timepoint interactions predicting RT-BOLD relationships (Figure 2, Table 2, 3D Neuroimaging Data). All nine regions also showed significant main effects of timepoint (all p s < .0001) and no effects of, or interactions with, condition or age (all p s > .12). Figure 3 presents results from the right IFG as an exemplar of the observed effects. HVs showed an early negative relationship between BOLD activity and RT, followed by a later positive relationship. This suggests that in HVs, increasingly long RTs, relative to faster RTs, were associated with larger pre-stimulus dips in activity and then increasing activity later in the trial. This pattern was blunted in both AR and BP individuals (Figure 3a) at a moderately large effect size (group $\times$ timepoint $\eta_p^2 = 0.08$). An independent-samples t -test comparing BP and AR to HV individuals at the peak timepoint indicated a large effect ($t(104)=4.44$, $p<.001$, Cohen's $d = 0.87$).

Figure S4 shows RT-BOLD timecourses for the remaining regions. Regions in the right precuneus, right caudate, and right medial frontal gyrus extending into dorsal ACC all showed a similar pattern to the IFG. AR and BP individuals exhibited blunting of the later positive RT-BOLD relationship observed in HVs in the left MFG, left precuneus, left caudate, and right postcentral gyrus. AR and BP individuals also showed blunting of the early negative RT-BOLD relationship observed in HVs in the posterior cingulate. Average BOLD activity in all nine regions exhibited a typical hemodynamic response shape (e.g., Figure 3b).

Two additional regions showed a group $\times$ condition $\times$ timepoint effect (Figure S5). These results were driven largely by effects at single timepoints and did not clearly represent condition-specific group differences. As such, these results are presented in the Supplemental Information and are not discussed further in the main text.

In an exploratory follow-up analysis to further elucidate the relationship between group differences in brain activity and behavior, the RT-BOLD relationship in the IFG (at a peak timepoint 6.25s after stimulus onset) served as a partial mediator of group differences (BP and AR vs. HV individuals) in ISVRT (Figure 3d; $\beta=0.010$, 95% Confidence Interval = [0.002–0.020], Sobel $Z=2.08$, $p=.038$), controlling for age at scan (see Supplemental Information). Such mediation was also observed in the left precuneus, right medial frontal gyrus, right caudate, and left middle frontal gyrus. This exploratory analysis indicated that blunted RT-BOLD relationships may contribute to attention lapses and increased reaction time variability.

Post-hoc Control Analyses

As noted above, age was not a significant predictor in any of the regions showing a group $\times$ timepoint interaction. Peak RT-BOLD was not correlated with age in any of these regions and examination of loess curves did not suggest non-linear trends (Figure S6). Further, group differences in ISVRT remained $p<.05$ significant in our age-restricted subsample (Table S2) and in the four separate post-hoc analyses excluding individuals with ADHD; AR

individuals with MDD; non-euthymic individuals; or medicated AR individuals (Table S4). All group $\times$ timepoint interactions predicting RT-BOLD relationships remained significant ($p < .05$) with these exclusions (details in Supplemental Information).

Discussion

While attentional deficits may represent a BP endophenotype (10), no prior studies have compared attention-related neural activity across low-risk, at-risk, and BP individuals. Here, we found that both BP and AR individuals exhibited increased ISVRT, a potential behavioral endophenotype. This confirms our hypothesis and is consistent with prior ISVRT studies assessed using different behavioral tasks. Second and most importantly, neural correlates of ISVRT also differed among these groups. Specifically, while the relationships between trial-wise RT and brain activity in the healthy, low-risk individuals here resembled those reported previously in healthy adults (27), both AR and BP individuals showed large pre-stimulus blunting and blunted compensatory fronto-cingulate activity, confirming our main hypotheses, in addition to alterations in other regions. We did not confirm our hypotheses regarding default mode RT-BOLD. Finally, blunted RT-BOLD partially mediated increased ISVRT in AR and BP individuals, mapping potential neural contributions to attention lapses.

These results link increased ISVRT and blunted RT-BOLD relationships both to expression of, and risk for, BP—two criteria of an endophenotype. Further, consistent with the state-independence criterion for endophenotypes, increased ISVRT and RT-BOLD differences were present during euthymia and therefore were not secondary to the acute pathophysiology of a depressed or manic state. Two notable features of our study are 1) that our sample included at-risk individuals within the age range of greatest risk for BP onset and 2) that we found matched perturbations in BP and AR individuals that were of large effect size. Thus, these neural patterns in AR individuals are more likely to be markers of risk for BP rather than resilience; such a differentiation can only be made in the few studies, such as ours, that compare both BP and AR individuals to HVs. Of note, while various neural mechanisms contribute to attentional lapses, in the current study, all of the regions that showed group differences in RT-BOLD associations showed nearly identical patterns in AR and BP individuals. This indicates that the same neural underpinnings likely contribute to observed behavioral deficits in both AR and BP individuals, again supporting these as potential endophenotypes.

Our results also capitalize on advances in fMRI analytic methods, which allow precise quantification of brain-behavior relationships. Here, we used a technique known as “amplitude modulation” to examine RT-BOLD relationships in the context of trial-by-trial variability. Where standard BOLD analyses averaging across trials cannot examine trial-by-trial effects, this approach allows us to precisely assess the neural underpinnings of RT variability. In fact, while we identified large group differences in RT-BOLD, our data revealed few meaningful between-group differences when traditional analytic approaches were used, again highlighting the importance of examining amplitude modulation in this study.

Importantly, the pattern of RT-BOLD results in the current study among healthy, low-risk individuals replicates patterns found previously in adults (27). Specifically, lapses in attention that are thought to generate long RT trials were associated with a pre-stimulus dip in activity followed by a later increase in activity in the ACC, MFG, and IFG. Drawing on biased-competition models of attention, Weissman et al. (2006) suggested that long RT trials are associated with decreased frontal activity before a behaviorally relevant stimulus appears, followed by compensatory increases in activity. Both the dip in frontal activity and mobilization of compensatory mechanisms were blunted in AR and BP individuals, compared to healthy individuals, in the right IFG, medial frontal gyrus/dorsal ACC, right caudate, and right precuneus. Additionally, deficits in compensatory attentional mechanisms were observed in the left precuneus, left MFG, left caudate, and right postcentral gyrus, all showing blunted peak RT-BOLD relationships in AR and BP individuals.

None of the regions identified in our analyses displayed task-related deactivation. Hence, we found no evidence that attentional lapses in BP reflect exaggerated difficulties inhibiting default mode network functioning. However, increased ISVRT has been related to decreased suppression of default mode network activity in ADHD (50), potentially suggesting different mechanisms underlying attentional deficits in these disorders.

Of note, studies of adults and children with BP often implicate similar regions to the ones identified here, including the IFG, MFG, ACC, and striatum, during sustained attention tasks (51) and across a variety of cognitive and emotional tasks (52–54). Meta-analyses of fMRI studies in BP indicate consistent differences in neural activity across paradigms in these regions as well (52–54). However, to our knowledge only one neuroimaging study has examined neural activity in individuals with a parental history of BP (or schizophrenia) during a sustained attention task (CPT) (55). This study found altered activity in the basal ganglia, particularly in the caudate, as well as frontal and parietal regions. Interestingly, the IFG has been quite consistently implicated in a variety of both functional and structural studies in BP and risk for BP, e.g., (56–59). In resting state functional connectivity studies, the IFG, as well as regions of the MFG and superior parietal regions, have been identified as part of a fronto-parietal control network (60). This network is suggested to implement rapid adaptive task control on a trial-by-trial timescale, as opposed to the more stable control/set maintenance mediated by the cingulo-opercular network (61). This formulation is germane to our findings, where we see alterations in trial-by-trial associations between fronto-parietal network activity and reaction times in AR and BP individuals. Thus, our results are consistent with dysfunction in adaptive attentional control and rapid online attention orienting as a potential endophenotype for BP.

Limitations

First, our sample spanned a wide age range from childhood through young adulthood, limiting our ability to make claims about whether the observed group differences were specific to any developmental window. Age-related effects have been identified previously in healthy individuals with this paradigm (32). However, age was not a significant covariate predicting RT-BOLD in any region that showed group differences, and all results held in an

age-restricted sample. That said, examining this wider age range could reduce our power to detect group differences and contribute to false negative results.

Next, we did not have a sufficient sample of unmedicated BP individuals to assess associations between medication use and behavior or brain activity. Importantly, no participants were on stimulants at the time of scan, as stimulants may influence RT distributions (62, 63). Further, our results held when comparing unmedicated AR and healthy individuals. Our results held when excluding BP participants with high YMRS/CDRS scores, supporting a state-independent endophenotype. However, characterizing mood only within a few days of scan limited our ability to establish firmly the presence of euthymia. Finally, the AR and BP individuals exhibited a variety of lifetime diagnoses. Confounding variables could include ADHD, which has been associated with increased ISVRT (64), and MDD among AR individuals, which may be the first manifestation of BP. However, post-hoc tests indicated that our results were not limited to, or driven by, individuals with ADHD or AR individuals with MDD. As we did not have sufficient sample sizes to fully test effects of or interactions with these factors, these will be important to examine in future work.

Conclusions and Future Directions

The current results suggest that increased ISVRT and blunted RT-BOLD may be useful endophenotypes for BP. It will be important to replicate this in independent sample and across other behavioral paradigms. Identifying behavioral and neural endophenotypes may aid in early identification of at-risk populations and in the development and evaluation of novel treatments targeting attentional deficits. While ISVRT has been suggested to be heritable (2), future work will need to assess the heritability of RT-BOLD associations, whether increased ISVRT and aberrant RT-BOLD associations predict the development of BP, and the specificity of these deficits to BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Group Differences in Intra-Subject Variability in Reaction Time

This figure presents estimated marginal means and standard errors (S.E.) for ISVRT from a repeated measures ANCOVA examining effects of group and condition controlling for age. There were no differences between the congruent (Con: open circles) and incongruent (Inc: filled circles) conditions. At-risk (AR: blue) and bipolar (BP: red) individuals showed increased ISVRT relative to healthy volunteers (HV: green).

Figure 2. Group × Timepoint Effects on RT-BOLD Relationships

This figure presents the regions that showed a significant group × timepoint interaction predicting RT-BOLD relationships (amplitude modulation). The peak coordinates, voxel extents, and further information about each region are presented in Table 2.

Figure 3. Group Differences in RT-BOLD in the Right Inferior Frontal Gyrus

This figure displays results from a region of right inferior frontal gyrus that showed a group $\times$ timepoint interaction predicting RT-BOLD relationships. (a) Estimated marginal means of percent signal change per second increase in MSRT and their standard errors from the repeated measures ANCOVA predicting RT-BOLD effects are displayed for healthy volunteers (green circles), at-risk individuals (blue triangles), and bipolar disorder individuals (red squares). Yellow shading indicates timepoints that showed $p < 0.05$ significant post-hoc t-test differences between any of the three groups. HV individuals showed an early negative RT-BOLD relationship followed by a later positive RT-BOLD association, which was blunted in AR and BP individuals. (b) Average BOLD activity in this region identified based on RT-BOLD differences did show a typical hemodynamic response shape. Average BOLD showed a main effect of timepoint ($F(3.51, 361.40) = 90.17, p < .001, \eta_p^2 = 0.34$) but did not show a group $\times$ timepoint interaction ($F(3.51, 361.40) = 0.58, p = .77, \eta_p^2 = 0.006$) or a group $\times$ condition $\times$ timepoint interaction ($F(3.51, 361.40) = 0.48, p = .87, \eta_p^2 = 0.001$). This was expected as this region was not identified in the whole brain analysis of average BOLD. The other eight regions identified from the RT-BOLD analyses showed similar average BOLD responses as well. (c) A sagittal slice through the peak of the IFG region is shown. (d) Mediation results indicated that RT-BOLD effects in the IFG (at a peak timepoint 6.25s after stimulus onset) are a significant partial mediator of group differences (BP and AR individuals as compared to HV individuals) in ISVRT. CI=confidence interval.

Table 1**Participant Characteristics**

	HV (N=53)	AR (N=29)	BD (N=24)	Comparison
Sex, N (%) female	32 (60.40%)	14 (48.30%)	15 (62.50%)	$\chi^2=1.44$, $p=.49$
Age in years, Mean (SD)	18.72 (4.09)	14.88 (3.47)	19.10 (3.77)	F=11.17, $p<.001$, $\eta^2_p=.08$
IQ, Mean (SD) ^a	115.14 (11.87)	110.72 (10.42)	109.75 (12.29)	F=2.33, $p=.10$, $\eta^2_p=.04$
PARS, Mean (SD) ^b	-	6.68 (5.94)	9.50 (7.72)	$t=1.68$, $p=.19$
CGAS/GAF, Mean (SD) ^b	-	77.55 (16.94)	57.92 (11.31)	$t=-4.85$, $p<.001$
YMRS, Mean (SD) ^b	-	1.69 (2.58)	4.00 (4.87)	$t=2.09$, $p=.04$
CDRS, Mean (SD) ^b	-	21.00 (4.68)	24.40 (8.49)	$t=1.52$, $p=.14$
SIGH-SAD, Mean (SD) ^b	-	1.00 (1.15)	5.43 (6.64)	$t=1.30$, $p=.21$
Current mood, N ^c				$\chi^2=6.67$, $p=.04$
Manic	-	0	0	
Hypomanic	-	0	2	
Mixed	-	0	0	
Depressed	-	0	3	
Euthymic	-	29	19	
Lifetime diagnoses, N				
MDD	-	5	-	
ADHD	-	3	9	$\chi^2=5.53$, $p=.02$
ODD or CD	-	4	8	$\chi^2=2.86$, $p=.09$
Any Anxiety Disorder	-	6	13	$\chi^2=6.40$, $p=.01$
Medication at scan, N ^d				
None	-	25	5	$\chi^2=18.02$, $p<.001$
Antipsychotic	-	0	14	
Lithium	-	1	10	
Antiepileptic	-	0	10	
Antidepressant	-	3	9	
Benzodiazepines	-	1	3	

Demographic and clinical data are summarized for each group, healthy volunteers (HV), at-risk individuals (AR), and bipolar disorder (BP) patients. ANOVAs, independent-samples t-tests, or chi-square tests were used to compare demographics across all three groups or to compare clinical scores, current mood, diagnoses, or medication use across the AR and BP groups. Significant group differences are marked in bold.

^aMissing IQ data from two HV cases

^bClinicians interviewed parents and AR and BP children/adolescents (<18 years old; N=25 AR, N=10 BP) using the CDRS, PARS, and CGAS. The YMRS was used to assess all AR and BP participants and the SIGH-SAD and GAF were used to assess AR and BP participants over 18 years old (N=4 AR, N=14 BP). CGAS and GAF scores are combined here as one variable.

^cCurrent mood was defined based on the YMRS, and on the CDRS (<18 years old) or SIGH-SAD (≥18 years old). Euthymia was defined as YMRS ≤12 and CDRS ≤40 or SIGH-SAD ≤20. Depression was defined as YMRS ≥12 and CDRS >40 or SIGH-SAD >20. Hypomania was defined as 12 < YMRS ≤26 and CDRS ≤40 or SIGH-SAD ≤20. Mania was defined as YMRS ≥26 and CDRS ≤40 or SIGH-SAD ≤20. Mixed State as: YMRS ≥12 and CDRS >40 or YMRS >12. The YMRS addressed mood for the prior two days; the CDRS addressed mood for the prior week.

^dMedications *at scan*- 5 BP participants were taking stimulants but were withheld for scan

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Table 2**Group $\times$ Time Interactions Predicting RT-BOLD Relationships**

Region	x	y	z	Voxels	BA	F	η_p^2	Group Differences
Right Inferior Frontal Gyrus	37	34	14	248	46/9	4.72	0.08	HV>AR=BD
Left Precuneus	-23	-57	42	169	7	4.56	0.08	HV>AR=BD
Right Medial Frontal Gyrus/Anterior Cingulate	5	13	45	168	6/23	3.90	0.07	HV>AR=BD
Right Posterior Cingulate	9	-33	31	112	23	3.98	0.07	HV=AR=BD
Left Middle Frontal Gyrus	-47	24	28	90	46	3.15	0.06	HV>BD
Right Caudate Body	12	-5	21	90	-	3.50	0.06	HV>AR=BD
Right Precuneus	19	-61	28	72	31	4.12	0.07	HV>AR=BD
Right Postcentral Gyrus	54	-26	38	47	9	3.08	0.06	HV>AR=BD
Left Caudate Body	-9	6	10	37	-	3.25	0.06	HV>BD

Regions showing significant effects on RT-BOLD relationships (amplitude modulation) in a whole brain analysis are presented here. Coordinates (x, y, z) are presented for the peak voxel in each region as well as the number of voxels exceeding the whole brain threshold. The Brodmann area (BA) for each region is also presented. The F-statistic and partial eta squared (η_p^2) of the group $\times$ timepoint interaction of interest were calculated on activity averaged across the region. All group $\times$ time interactions and main effects of time were significant at $p < .001$; none of these regions showed a significant effect of age $\times$ time or age $\times$ condition $\times$ time (all $ps > .12$). Post-hoc pairwise t-tests were run at each timepoint. Differences at the peak timepoint (6.25 seconds after stimulus onset) are described here to summarize differences between groups; significant effects at a Bonferroni corrected $p < .017$ (.05/3) are noted in the Group Differences column. Note that while there were no significant differences at this peak timepoint for the right posterior cingulate, group differences were noted earlier in the timecourse, e.g. 2.5 seconds after stimulus onset (HV<AR=BP).