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

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ABSTRACT

BACKGROUND: Few neuroimaging studies compare individuals affected with bipolar disorder (BP), at high familial risk of 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 present study examined 8- to 25-year-old individuals ($n = 106$) 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 intrasubject variability in reaction time were examined, and a sophisticated fMRI analytic approach was used to quantify precisely trialwise associations between reaction time and brain activity. The latter has not been examined previously in BP or risk of BP.

RESULTS: Relative to healthy individuals, those with BP or at risk for BP exhibited increased reaction time variability ($F_{2,102} = 4.26$, $p = .02$, $\eta_p^2 = .08$). Importantly, we identified blunted relationships between trialwise variation in reaction time and brain activity in the inferior and middle frontal gyri, precuneus, cingulate cortex, caudate, and postcentral gyrus (all regions: $p < .001$, $\eta_p^2 > .06$) in both at-risk and BP individuals compared with healthy, low-risk individuals. This blunting partially mediated group differences in reaction time variability ($\beta = .010$, 95% confidence interval 0.002 to 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: Attention, Bipolar disorder, fMRI, Inferior frontal gyrus, Intra-individual variability, Reaction time, Risk

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Intrasubject 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. Whereas most developmental psychopathology studies examine ISVRT behavior in attention-deficit/hyperactivity disorder (ADHD) (5–7), the few studies on youth with or at risk for BP find increased ISVRT, compared with healthy, low-risk youths (8,9). The present 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 at-risk (AR) individuals with 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 of BP examine youth or young adults (JL Wiggins, Ph.D., *et al.,* unpublished data, 2016) (11–15); the other half examines middle-aged adults (16–22). More studies in youth are needed, particularly because middle-aged relatives of BP patients are beyond the typical age of BP onset (23). Thus, studies in older age groups likely include many resilient rather than AR individuals.

Whereas 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 (24,25). 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 blood

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oxygen 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 (26–28). 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.* (26) note trial-by-trial associations between attentional lapses and 1) prestimulus 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 (29,30) and in youth versus adults (31). The present study builds on this uniquely powerful research strategy to examine BP.

Examining youth and young adults with or at risk for BP, we tested two hypotheses addressing attentional variability as a potential BP endophenotype. First, we tested 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 used brain imaging to examine neural correlates of this potential behavioral endophenotype, using the analytic method described above to quantify precisely trialwise 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 before stimulus presentation, deficits in compensatory frontocingulate 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 (HVs) 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 (32). Adult participants were assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (33). Comorbid diagnoses were assigned based on symptoms present during euthymia. AR 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 Structured Clinical Interview for DSM-IV-TR Axis I Disorders or the Diagnostic Interview for Genetic Studies (34), and sibling diagnoses of BP were confirmed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version. 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 (aged <18 years; $n = 25$ AR, $n = 10$ BP) and their guardians separately, or AR and BP participants older than 18 years ($n = 4$ AR, $n = 14$ BP), within 1 week of scanning using several measures. Depressive symptoms were assessed in children/adolescents using the Children's Depression Rating Scale (35) and in adults using the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (36). Anxiety symptoms were assessed in children/adolescents using the Pediatric Anxiety Rating Scale (37). General functioning was assessed in children/adolescents using the Children's Global Assessment Scale (38) and in adults using the Global Assessment of Function (39). The Young Mania Rating Scale (40) 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 (41), 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. AR individuals were not excluded for mood pathology (other than BP or disruptive mood dysregulation disorder) to avoid recruiting a particularly resilient group (11,42). Sixteen of the AR individuals had no lifetime diagnoses (Table 1).

Of the 121 individuals (aged 8–25 years) 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 ($X^2_2 = 0.39$, $p = .82$). The final sample included 106 participants: 53 HVs (aged 9.5–24.6 years), 29 AR individuals (aged 8.9–20.6 years), and 24 individuals with BP (aged 12.8–24.6 years).

In-Scanner Behavioral Paradigm

Participants performed a modified global-local selective attention task (26). The task included four stimuli (Supplemental 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), and 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 200 ms, followed by 2300 ms 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