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Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder

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Abstract

Objective—To examine conflict monitoring and conflict-driven adaptation in individuals at familial risk for developing bipolar disorder.

Methods—We recruited 24 adolescents who had a parent with bipolar disorder and 23 adolescents with healthy parents. Participants completed an arrow version of the Eriksen Flanker Task that included trials with three levels of conflict: neutral, congruent, and incongruent flanks. Differences in performance were explored based upon the level of conflict in the current and previous trials.

Results—Individuals at risk for developing bipolar disorder performed more slowly than youth with healthy parents in all trials. Analyses evaluating sequential effects revealed that at-risk subjects responded more slowly than youth of healthy parents for all trial types when preceded by an incongruent trial, for incongruent trials preceded by congruent trials, and for neutral and congruent trials when preceded by neutral trials. In contrast to the comparison group, at-risk adolescents failed to display a response time advantage for incongruent trials preceded by an incongruent trial. When removing subjects with attention-deficit hyperactivity disorder (ADHD), differences between groups in response time fell below significant level, but a difference in sequence modulation remained significant. Subjects at risk for bipolar disorder also displayed greater intra-subject response time variability for incongruent and congruent trials compared with the comparison adolescents. No differences in response accuracy were observed between groups.

Conclusions—Adolescents at risk for developing bipolar disorder displayed specific deficits in cognitive flexibility, which might be useful as a potential marker related to the development of bipolar disorder.

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Disclosures

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Keywords

at risk; bipolar disorder; conflict-driven adaptation; conflict monitoring; intra-subject variability in response time

Bipolar disorder is a highly heritable illness, with genetic influences explaining 60–85% of risk variance (1). However, specific susceptibility genes or neurobiological markers remain unknown. In recent years, genetic and behavioral neuroscience has attempted to define endophenotypes that encompass deficits that are heritable, state-independent, and cosegregated with illness, as well as those which occur at higher rates in unaffected relatives than the general population (2, 3). Plausible endophenotype candidates in bipolar disorder include impairments in specific neurocognitive domains.

Cognitive impairments in individuals with bipolar disorder were traditionally thought of as mild and limited to acute mood episodes; however, a growing body of evidence challenges this assumption. At least three recent meta-analyses in euthymic adults with bipolar disorder (4–6) and two in youths with bipolar disorder have identified several cognitive impairments, particularly in attention, processing speed, and other aspects of executive function (7, 8). Some studies have suggested that medication exposure has an effect on cognition in both adult (9) and pediatric bipolar disorder subjects (10), while others have suggested no neurocognitive differences in euthymic unmedicated pediatric bipolar disorder subjects (11). Thus, studies of cognitive impairment in youths and adults with bipolar disorder cannot fully dissociate possible effects of illness chronicity and medication exposure. Studying youth at familial risk for developing bipolar disorder (i.e., with a parent who has bipolar disorder) could facilitate identifying cognitive endophenotypes, yet few studies have examined neurocognitive function in this population. Nonetheless, recent studies suggest that children of bipolar disorder patients demonstrate specific deficits in executive function, particularly in tasks assessing cognitive interference and flexibility (12, 13).

Cognitive interference occurs when task-irrelevant background information impedes processing task-relevant information that forms the current focus of attention (14). Cognitive conflict may be best described as a special instance of cognitive interference in which task-irrelevant information induces incongruent or incompatible mental representations (15). Given this theoretical approach, selecting task-relevant over task-irrelevant information may be thought of as a core process in the resolution of cognitive interference, and the main goal of conflict monitoring (16). Similarly, changes in processing speed with shifting levels of conflict represent a measure of conflict-driven adaptation (17).

In the current study, we examined conflict monitoring and conflict-driven adaptation in youths at risk for bipolar disorder using an arrow version of the Eriksen Flanker Task (EFT). We hypothesized that youths at risk for bipolar disorder would exhibit deficits in conflict monitoring and conflict-driven adaptation. Additionally, we predicted that youths at risk for developing bipolar disorder would be more susceptible to interference, exhibit increased behavioral inconsistencies as measured by increased variability of response time, and show less flexible cognitive adaptation to shifting levels of conflict than healthy controls.

Methods

Study participants

Twenty-four adolescents (age 10–20 years) at risk of developing bipolar disorder were recruited from an ongoing longitudinal study assessing the neurodevelopment of adolescents with familial risk for bipolar disorder. At-risk (AR) subjects were defined by having at least

one parent with bipolar I disorder and no current or past history of any mood or psychotic disorder in themselves. Twenty-three comparison subjects (HC) with healthy parents, with no Axis I psychiatric disorder, and no first- or second-degree relative with any mood or psychotic disorder, were also recruited. Subjects in both groups were excluded for any lifetime history of substance use disorder or a pervasive developmental disorder, a total IQ score < 80 [as determined by the Wechsler Abbreviated Scale of Intelligence (WASI)], a loss of consciousness of > 10 minutes, or any unstable neurological or medical illness. All subjects were medication-free at the time of testing.

The study was approved by the University of Cincinnati's Institutional Review Board (Cincinnati, OH, USA). Participants who were 18 years or older signed informed consent, while those younger than 18 years of age signed assent forms and their parent or legal guardian signed informed consent documents.

Diagnostic assessment

Parental diagnoses were assessed using the Structured Clinical Interview for DSM-IV Patient Version (SCID-IP), administered by trained interviewers with high inter-rater reliability ($\kappa > 0.90$). The Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH U K-SADS) was administered to participants by trained interviewers ($\kappa > 0.90$) blind to the group status, in order to determine the presence of Axis I psychiatric diagnoses in the children and adolescents. Trained clinicians with good inter-rater reliability [intraclass correlation (ICC) > 0.85] evaluated severity of manic and depressive symptoms using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating scale (HDRS), respectively.

EFT

The EFT has been repeatedly used to study conflict monitoring and cognitive flexibility. In an arrow version of the EFT (18), a target arrow is pointing to the left or right and is flanked by squares (neutral condition: $\blacksquare \rightarrow \blacksquare$), or by additional arrows pointing either in the same direction (congruent condition: $\rightarrow \rightarrow \rightarrow \rightarrow$), or in the opposite direction (incongruent condition: $\leftarrow \leftarrow \rightarrow \leftarrow$). Subjects were asked to indicate the direction in which the central arrow is pointing by pressing, with each hand's index finger, on a keyboard button labeled with an arrow pointing to the right or left.

In the EFT, targets with incongruent flankers show a slower reaction time, compared to targets with congruent and neutral flankers (19). Moreover, response time in the EFT has been shown to be sequence modulated (20), i.e., response time to the current trial (n) is dependent on the level of conflict in the preceding trial (n-1). Response time to congruent trials following congruent or neutral trials (cC or nC, respectively) are faster than congruent trials that follow incongruent trials (iC) and response time to incongruent trials following incongruent trial (iI) are generally faster than incongruent trials following neutral (nI) or congruent trials (cI); an effect also known as conflict-driven adaptation (21).

Each block of the task was presented in the following sequence: a signal consisting of a fixation cross (500 msec), followed by the task-related stimulus (1000 msec), and then a blank black screen (1500 msec). Three trial types were presented: neutral, congruent, and incongruent. Participants were required to press the right or left key corresponding to the direction of the target arrow as fast and accurately as possible. The task commenced with a practice run (30 blocks, 10 of each trial type), followed by the testing condition consisting of 130 blocks (44 neutral, 43 congruent, and 43 incongruent) presented in a fixed pseudorandom fashion. The task was set up in a way that 22.5% of the stimuli were non-

shift trials (nN, cC, and iI) and 77.5% shift trials (iN, cN, iC, nC, nI, and cI). All participants completed the task in a quiet, well-lit room and with the same laptop computer.

Based on our previous studies, responses that were less than 250 msec after the stimulus appeared were considered anticipatory errors. Response times that were two standard deviations above the group mean were considered omission errors. Accuracy rates for the entire trial and by trial type were calculated. Both omission and anticipatory errors were removed from data analyses; groups did not differ in rates of omission and anticipatory errors ($p = 0.68$ and $p = 0.8$, respectively). Subjects with more than 25% omission errors, or 30% total errors were considered to be insufficiently engaged with the task and were excluded from further analysis (AR group $n = 2$; HC group $n = 3$). Intra-subject variability in response time (ISV-RT), as a measure of behavioral inconsistency, was calculated using the standard deviation of the mean response time for each individual for the whole task, for each trial type and the combination of current trial type, and previous trial type.

Statistical analysis

All statistical analyses were performed using Predictive Analytics SoftWare Statistics version 18.0. Group differences in demographic and clinical variables were measured using independent sample t -tests and chi-squared tests.

Linear mixed models were used to assess for group differences in performance in the EFT. Linear mixed models allow for correlated data to be analyzed, hence all 130 observations per individual were considered in the model. The model was specified taking into account block and subject as repeated measurements with a within-subject effect, and setting response time or ISV-RT as the dependent variable, group as a fixed effects, and WASI score as covariates. The model also analyzed the fixed effects of current and previous trial type (higher order interaction term group $\times$ previous trial type $\times$ current trial type, with all other lower order interaction terms in the model); this allows testing for differences in interference, sequence modulating effects, and conflict-driven adaptation. The covariance matrix structure of the residual errors of the repeated observations was selected through the Akaike's Information Criterion. Denominator degrees of freedom were calculated with Satterthwaite's approximation. Differences in response time and ISV-RT between groups were calculated through the estimated marginal means of the fitted model with a sequentially step-down rejective Bonferroni procedure to adjust for multiple testing.

In a secondary analysis, AR subjects with a lifetime diagnosis of attention-deficit hyperactivity disorder (ADHD) were excluded to ensure differences between groups were not limited to the presence of ADHD.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the study participants are presented in Table 1. Both AR and HC subjects were medication free (AR with ADHD, four patients had a prior history of medication use: two had taken d-amphetamine and two had taken methylphenidate). IQ scores were higher in the HC subjects as compared to the AR subjects, although the difference did not reach statistical significance ($p = 0.09$). To evaluate the potential impact of IQ on the EFT performance, we tested the correlation between response time and WASI score. WASI score was inversely correlated with mean response time ($|r| = -0.45$, $p < 0.0001$) and was hence included as a covariate in the linear mixed models.

Eight subjects in the AR group (36%) met DSM-IV criteria for ADHD. AR individuals displayed higher scores on both the YMRS ($p = 0.05$) and HDRS ($p = 0.001$). However,

mean scores for both groups were well below clinical significance and neither was associated with performance (YMRS and response time $|r| = -0.11$, $p = 0.5$; HDRS and response time $|r| = -0.04$, $p = 0.8$; YMRS and accuracy rate $|r| = 0.04$, $p = 0.8$; HDRS and accuracy rate $|r| = 0.1$, $p = 0.5$). Thus, rating scale scores were not included in the models as covariates.

EFT

Proportion of correct responses did not differ between groups. Subjects in both groups responded slower to incongruent flanks than congruent and neutral flanks [$F_{(2,3381)} = 294$, $p < 0.001$]. Examining the response time to the current trial, AR subjects performed slower throughout the EFT [$F_{(1,803)} = 20$, $p < 0.001$] (Table 2). Specifically, AR subjects displayed slower response times to neutral [$F_{(1,1771)} = 17$, $p < 0.001$], congruent [$F_{(1,1809)} = 15$, $p < 0.001$], and incongruent flanks [$F_{(1,1987)} = 8$, $p = 0.004$] compared to HC subjects. There was no statistically significant group effect for current trial type [interaction group $\times$ current trial: $F_{(2,3386)} = 0.92$, $p = 0.4$]. Examining the effect of previous trial type in the response to the current trial (Table 3), we found that in both groups, there was a significant main effect of previous trial type on response time to the current trial [$F_{(2,4113)} = 5$, $p = 0.008$]. Current trial type was also significantly associated with response time within each group [$F_{(2,3875)} = 279.5$; $p < 0.0001$]. A sequence modulation of response time was observed in both groups [interaction term current trial $\times$ previous trial $F_{(4,3734)} = 11$, $p < 0.001$].

A significant difference between groups in the sequence modulation of response time was detected through the interaction between previous trial type $\times$ current trial type $\times$ group [$F_{(4,3738)} = 3$, $p = 0.03$]. Specifically, post-hoc analyses revealed that the AR group was significantly slower than the HC group (Table 3) in response to neutral, congruent, and incongruent trials when preceded by an incongruent trial ($p = 0.006$; $p = 0.02$, and $p = 0.03$, respectively). AR subjects were also slower than HC in neutral and congruent trials when preceded by neutral trials ($p < 0.0001$ and $p < 0.001$, respectively) and to incongruent trials when preceded by congruent trials ($p < 0.01$).

When specifically exploring the conflict-driven adaptation effects we found that incongruent trials preceded by incongruent trials were faster than incongruent trials preceded by neutral trials in the HC group ($p = 0.02$), but not in the AR group ($p = 1.0$). In both groups, neutral trials that were preceded by neutral trials were significantly faster than neutral trials that were preceded by incongruent trials ($p < 0.001$ both groups) but the difference was non-significantly larger in the HC group ($p = 0.06$). No statistically significant differences within groups were detected when comparing congruent trials preceded by congruent trials, congruent trials preceded by neutral trials and congruent trials when preceded by incongruent trials.

A significant group effect for ISV-RT was detected [$F_{(1,39.1)} = 6.8$, $p = 0.01$]. Post-hoc analyses indicated that AR subjects showed larger ISV-RT (Table 2 and Fig. 1) in trials with congruent ($p = 0.03$) and incongruent flanks ($p = 0.002$) but not in trials with neutral flanks ($p = 0.2$). No sequence modulation of ISV-RT was detected.

When removing individuals with a lifetime diagnoses of ADHD, difference between groups in response time to the current trial type fell below the significant level [$F_{(1,642)} = 2.2$, $p = 0.1$]. However, the sequence modulating effect was still present within each group [interaction previous trial type $\times$ current trial type: $F_{(4,3010)} = 13.1$, $p < 0.001$], and it was significantly different between groups [group $\times$ previous trial type $\times$ current trial type: $F_{(4,3001)} = 3.3$, $p = 0.01$]. Specifically HC individuals displayed faster responses to incongruent trials when preceded by incongruent trials than when preceded by either neutral

or congruent trials ($p = 0.03$ and $p = 0.04$, respectively), whereas AR failed to display this conflict-driven adaptation effect ($p > 0.10$ in both comparisons).

With subjects with ADHD removed, group differences in ISV-RT remained significant [$F_{(1,28.6)} = 4.27$, $p = 0.048$]. Specifically, ISV-RT was significantly larger for AR individuals in incongruent trials ($p = 0.005$) and was marginally larger in congruent trials ($p = 0.07$). No sequence-modulating effect in ISV-RT in both groups was detected [$F_{(4,30.5)} = 1.8$, $p = 0.1$] nor between groups [$F_{(4,30.6)} = 0.4$, $p = 0.8$].

Discussion

In this study we found that adolescents with a familial risk for bipolar disorder performed slower overall, and displayed larger variability in response time to targets with higher levels of conflict than adolescents without a familial risk. Exploring the sequential effect on response time, we also found that at-risk individuals showed evidence of abnormal conflict-driven adaptation: incongruent trials preceded by incongruent trials were not significantly faster than incongruent trials preceded by neutral or congruent trials. We also found that AR youths were unable to adapt to shifting levels of conflict; they did not demonstrate a significant response time advantage in other trials with repeating stimuli, and performed more slowly in trials shifting away from conflict; this effect was independent of ADHD. These findings are similar to data from previous studies examining similar neurocognitive domains, such as the Stroop Color-Word Test (22, 23).

Several investigators have proposed a neurobiological model for conflict monitoring and conflict-driven adaptation (24). Specifically, the anterior cingulate cortex (ACC) is activated by the detection of conflict between task-relevant information (target stimuli) and task-irrelevant information (flankers) and conveys this information to the dorsolateral prefrontal cortex (DLPFC) (25–28). The DLPFC then adjusts the level of cognitive control to the subsequent trial, leading to a better resolution of the conflict and consequently enhance performance should the subject experience conflict again. Conflict-driven adaptation in this model is produced by an enhancement of the processing of task-relevant information and a parallel inhibition of the processing of task-irrelevant information. Therefore, after a task with a high level of conflict (incongruent trial) the response to a subsequent trial with a high level of conflict is faster and more accurate than a trial with a high level of conflict preceded by a trial with a low level of conflict that did not activate the conflict-driven adaptation process (29, 30). We observed that AR subjects lacked this conflict-driven adaptation, suggesting dysfunction in ACC and DLPFC brain regions. These same regions have been shown to be associated with the disorder in previous studies (31–34).

Our findings in response time did not replicate a recent study using a Flanker Continuous Performance Tests in AR subjects (35). Differences in response time between AR and HC were not detected in that study, although an increase in errors in AR subjects was identified. One possible explanation for this discrepancy is the difference in task presentation; it is plausible that the more rapid Flanker Continuous Performance Tests used in the previous study yielded more errors, which mitigated differences in response times overall. Despite these differences, our study did replicate the finding in this same study of increased intra-subject variability in response time even when eliminating subjects with ADHD.

Increased ISV-RT may reflect deficits in sustained attention (36). Indeed, deficits in selective attention have been observed in relatives of patients with bipolar disorder on some studies (8, 37) and in euthymic patients with bipolar disorder (38, 39). It is possible that these deficits may relate to abnormalities in the neural mechanisms regulating sustained attention. A functional magnetic resonance imaging study in healthy individuals found that brief

lapses of attention began with a reduced prestimulus activity of the right inferior frontal gyrus, the right medial frontal gyrus, and the ACC, followed by a reduced task-induced deactivation of the default mode network, and an increased activity in the ACC after the lapses in attention had occurred (40). In bipolar disorder, a functional magnetic resonance imaging study performed by our group, which addressed sustained attention in mania, showed that sustained attention deficits in bipolar disorder are accompanied by regional activation decrements in the DLPFC, a stable overactivation of the amygdala during prolonged vigils and a striatal and thalamic deactivation which is interpreted as a loss of amygdala modulation by the ventrolateral prefrontal-subcortical circuit (41). To date, we do not know of any neuroimaging study that has focused on the mechanisms mediating ISV-RT in bipolar disorder or in individuals at risk for bipolar disorder. An alternative explanation to a deficit sustained attention may be that increased ISV-RT represents a neurocognitive marker of stress reactivity. Stress reactivity is a risk indicator for mood disorders that is mediated by genetic traits (42) but also heavily influenced by environmental factors (43). Studies in bipolar disorder offspring have highlighted the presence of increased stress reactivity (44, 45). An increase in response time variability among ADHD patients has been found to be associated with increased cortisol levels after stress (46). Moreover, response time variability has been associated with diminished attentional control exerted by the prefrontal cortex during exposure to stress (47).

Additionally, under stress the prefrontal cortex activity is closely related to activity of the hypothalamic pituitary adrenal axis, and high levels of adrenergic activation have been shown to have a detrimental effect on attention performance (48, 49). So, it may be possible that response time variability and increased stress reactivity are closely related

The slower response times, larger intra-subject variability in response time and lack of conflict-driven adaptation that we observed in AR subjects may represent a potential marker of increased risk for bipolar disorder. Longitudinal studies in AR subjects are needed to identify whether lack of conflict-driven adaptation and increased ISV-RT translates into an increased risk for developing bipolar disorder over time. If this is the case, studying conflict-driven adaptation and increased ISV-RT may help clarify some of the neurobiological basis of this disorder as well as help develop early interventions.

Limitations

There are several limitations to our study including the small sample size which might have limited our ability to detect additional group differences. The AR group included several patients with ADHD. Children with ADHD are known to display specific disadvantages in the EFT including slower reaction time (50), increased ISV-RT (51), decreased accuracy, and monitoring ongoing behavior (52). Consequently, it is possible that differences observed between AR and HC subjects can be in part due to the presence of ADHD. In addition, our study did not include a group of subjects with bipolar disorder. This limits our ability to place our findings within the bipolar phenotype.

Future directions

There is a paucity of neurocognitive and neurobiological studies of individuals at risk for bipolar disorder. Using neuroimaging techniques to study conflict-driven adaptation may further clarify an endophenotype of bipolar disorder.

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Fig. 1.

Intra-subject variability in response time between at-risk subjects and healthy controls. AR = at-risk; HC = healthy controls. * $p < 0.05$.

Table 1

Demographic and clinical characteristics

	At-risk (n = 22)	Healthy controls (n = 20)
Age, years, mean (SD)	15 (3)	15 (3)
Sex, female, n (%)	10 (46)	9 (45)
Race, non-white, n (%)	5 (23)	4 (20)
WASI, mean (SD)	105 (10)	111 (13)
HDRS, mean (SD) ^a	5 (5)	1 (1)
YMRS, mean (SD) ^b	3 (4)	1 (2)

SD = standard deviation; WASI = Wechsler Abbreviated Scale of Intelligence; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

^a p < 0.001.

^b p < 0.05.

Table 2Performance in Eriksen Flanker task by trial type^a

	At-risk (n = 22)	Healthy controls (n = 20)
Proportion correct, mean (SD)		
Neutral	0.97 (0.05)	0.98 (0.04)
Congruent	0.98 (0.03)	0.97 (0.04)
Incongruent	0.93 (0.06)	0.95 (0.15)
Intrasubject variability, mean (95% CI)		
Neutral	65 (59–72)	59 (53–67)
Congruent ^b	69 (64–75)	59 (55–63)
Incongruent ^c	67 (61–72)	53 (49–60)
Response time, mean (SD)		
Neutral ^d	467 (71)	450 (34)
Congruent ^d	474 (67)	457 (42)
Incongruent ^c	516 (60)	503 (30)

SD = standard deviation; CI = confidence interval.

^aAnalysis covaried for IQ.^bp < 0.05.^cp < 0.01.^dp < 0.001.

Table 3

Eriksen Flanker Task estimated marginal mean response time (95% confidence intervals) by trial, considering previous trial type^a

Previous trial	Current trial	At-risk (n = 22)	Healthy controls (n = 20)
Neutral flank	Neutral ^b	458 (448–467)	428 (418–439)
	Congruent ^b	477 (469–484)	456 (447–464)
	Incongruent	514 (505–522)	511 (502–520)
Congruent flank	Neutral	460 (452–468)	449 (441–458)
	Congruent	464 (453–475)	449 (437–461)
	Incongruent ^c	522 (514–530)	503 (495–512)
Incongruent flank	Neutral ^c	479 (471–487)	462 (454–470)
	Congruent ^c	474 (468–481)	460 (451–466)
	Incongruent ^d	512 (502–523)	495 (488–501)

^a Estimated marginal means covariate for IQ.

^b p < 0.001.

^c p < 0.01.

^d p < 0.05.