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Increased intrasubject variability in response time in unaffected preschoolers at familial risk for bipolar disorder

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Abstract

Increased intrasubject variability in response time (ISVRT) is evident in healthy preschoolers at familial risk for bipolar disorder, suggesting it may be an endophenotype.

Keywords

Population at Risk; Bipolar Disorder; Endophenotype

1. Introduction

Attention deficits are a core, persistent feature of bipolar disorder (BD) (Torres et al., 2007) in children and adults (Fleck et al., 2005; Joseph et al., 2008). Intrasubject variability in response time (ISVRT) is a highly heritable (Kuntsi et al., 2006) measure of attention regulation. ISVRT measures variability in the duration of motor responses across trials, representing fluctuation in attention over time. Specifically, increased ISVRT is thought to result from intermittent attentional lapses that result in relatively long-RT trials. Thus, ISVRT serves as a direct, quantitative gauge of attention deficits. Increased ISVRT indicating attention dysregulation is present in BD regardless of mood state, medication, or comorbidity, and in unaffected, first-degree relatives (Bora et al., 2006; Brotman et al., 2009), supporting its potential role as a cognitively-based BD endophenotype (Gottesman and Gould, 2003).

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ISVRT has been examined in both school-aged and adult first-degree relatives of children and adults with BD (Bora et al., 2009; Brotman et al., 2009). However, extending studies to younger populations is essential; BD is a developmental disorder (Kessler et al., 2005) with roots in early brain development (Post et al., 1996). Identification of risk factors appearing early in development would facilitate prevention. However, research in preschool-age populations entails specific challenges. Specifically, such research requires specialized expertise in the clinical assessment of preschoolers in addition to age-appropriate paradigms to probe the constructs of interest (e.g., attention regulation). Few studies of preschool-aged at-risk BD populations exist, and most have focused on temperament and psychopathology (Birmaher et al., 2010; Hirshfeld-Becker et al., 2006), rather than cognitive processes.

We compared unaffected preschoolers at familial-risk for BD to healthy children on a developmentally-appropriate attentional flanker task to determine whether increased ISVRT is present in at-risk children at that early developmental stage.

2. Methods

Forty-nine children (3.5–6.5 years) participated: 15 at-risk for BD (at-risk, AR; first-degree relative with BD: 3 siblings, 12 parents, mean age 4.6±0.6y) and 34 not at-risk, healthy children (HC, 4.9±0.8y; Table S1). Subjects were not related. Informed consent/assent was obtained. The Preschool Aged Psychiatric Assessment (PAPA; (Egger et al., 2006)) was used to ascertain psychiatric diagnoses (data unavailable: 1 AR, 6 HC).

Preschoolers completed a 120 trial flanker task (McDermott et al., 2007), indicating the color of a center circle (red or green) by button press (for details, see Supplemental Information). Half the trials were congruent (center circle flanked by same-color circles), half were incongruent (flanked by opposite-color circles).

Evidence suggests measures of response time (RT) variability should control for differences in mean RT (Epstein et al., 2011); thus, we used coefficient of variation of RT (CV-RT, calculated as SD-RT/mean-RT) to measure ISVRT as the primary variable. Higher CV-RT values indicate more variability in response time during the task. Overall CV-RT for all trials was calculated, in addition to separate CV-RTs for congruent and incongruent trials. Independent-sample t-tests compared CV-RT, successful hits (%), and errors of omission (%). As a secondary analysis, CV-RTs were compared covarying for errors of omission, thereby controlling for differences in total number of analyzed trials.

3. Results

Groups did not differ on age, IQ, or sex (P's>0.13). Based on the PAPA assessment, no subject in either group met criteria for a psychiatric disorder. Trend differences emerged in performance measures: hits (AR<HC, P=0.08), errors of omission (AR>HC, P=0.05).

ISVRT, as measured by CV-RT, was greater for AR than HC on all trials (P=0.02), incongruent trials (P=0.01), and, at trend level for congruent trials (P=0.08) (Fig.1).

When covarying errors of omission, CV-RT for incongruent trials remained greater for AR than HC (P=0.03). Differences in CV-RT across all trials (P=0.14) and for congruent (P=0.90) became non-significant.

When AR with parent probands (n=12) were compared to the 34 HC, findings remained the same: CV-RT greater for AR than HC (total: P=0.04; incongruent: P=0.02; congruent: P=0.09).

4. Discussion

This study provides additional support that increased ISVRT may be an endophenotype for BD by documenting its presence in unaffected AR preschool-age relatives. Deficits at this early developmental stage suggest a close relationship between dysfunctional attention regulation and BD risk.

Increased ISVRT among AR subjects was observed across all trials, although more markedly during incongruent trials. The difference in ISVRT between AR and HC remained significant for incongruent trials after controlling for performance. Incongruent trials require greater attentional control than do congruent trials. Greater attentional task demands of the incongruent trials revealed deficits in young, at-risk children. These deficits may reflect inferior frontal gyrus dysfunction, as has been observed in school-age and adult AR for BD (Ladouceur et al., 2013; Roberts et al., 2013). Findings for the congruent trials are less clear; ISVRT was greater in AR at trend level, but not present when controlling for errors of omission. This may reflect a type II error; such an error may have resulted because of the small sample size, an important limitation of the study.

Although increased ISVRT has been proposed as a possible endophenotype of BD, the phenomenon has also been reported in patients with ADHD and their unaffected relatives (Epstein et al., 2011; Nigg et al., 2004) and thus is also a possible ADHD endophenotype. While comorbid ADHD is common in pediatric BD, attention deficits are present in BD with or without comorbid ADHD, and in unaffected relatives (Brotman et al., 2009). Therefore, attention deficits may be present in ADHD, BD, and possibly other developmental psychiatric disorders. Future research should attempt to differentiate the neural correlates of attention dysregulation associated with ADHD vs. BD in order to elucidate both shared and distinct pathophysiological mechanisms of these disorders. Such information would facilitate translational research, more accurate diagnosis, and more effective treatments for both illnesses.

BD is a chronic disease associated with high morbidity and mortality (Gale et al., 2012). Childhood-onset BD tends to be particularly severe and debilitating (Geller et al., 2004). To facilitate early identification and development of targeted treatments, it is essential to document endophenotypes identifiable in AR children at a very young age. This study provides further evidence that increased ISVRT may be a BD endophenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

Birmaher B, Axelson D, Goldstein B, Monk K, Kalas C, Obreja M, Hickey MB, Iyengar S, Brent D, Shamseddeen W, Diler R, Kupfer D. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). American Journal of Psychiatry. 2010; 167:321–330. [PubMed: 20080982]

Bora E, Vahip S, Akdeniz F. Sustained attention deficits in manic and euthymic patients with bipolar disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2006; 30:1097–1102. [PubMed: 16740350]

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. Journal of Affective Disorders. 2009; 113:1–20. [PubMed: 18684514]

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. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; 48:628–635. [PubMed: 19454918]

Egger HL, Erkanli A, Keeler G, Potts E, Walter BK, Angold A. Test-Retest Reliability of the Preschool Age Psychiatric Assessment (PAPA). Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45:538–549. [PubMed: 16601400]

Epstein JN, Langberg JM, Rosen PJ, Graham A, Narad ME, Antonini TN, Brinkman WB, Froehlich T, Simon JO, Altaye M. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. Neuropsychology. 2011; 25:427–441. [PubMed: 21463041]

Fleck DE, Shear PK, Strakowski SM. Processing efficiency and sustained attention in bipolar disorder. Journal of the International Neuropsychological Society. 2005; 11:49–57. [PubMed: 15686608]

Gale CR, Batty GD, Osborn DP, Tynelius P, Whitley E, Rasmussen F. Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men. Archives of General Psychiatry. 2012; 69:823–831. [PubMed: 22868936]

Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Archives of General Psychiatry. 2004; 61:459–467. [PubMed: 15123490]

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. The American journal of psychiatry. 2003; 160:636–645. [PubMed: 12668349]

Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF. Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study. Psychiatry Research. 2006; 145:155–167. [PubMed: 17083985]

Joseph MF, Frazier TW, Youngstrom EA, Soares JC. A quantitative and qualitative review of neurocognitive performance in pediatric bipolar disorder. Journal of Child and Adolescent Psychopharmacology. 2008; 18:595–605. [PubMed: 19108664]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry. 2005; 62:593–602. [PubMed: 15939837]

Kuntsi J, Rogers H, Swinard G, Börger N, van der Meere J, Rijsdijk F, Asherson P. Reaction time, inhibition, working memory and 'delay aversion' performance: genetic influences and their interpretation. Psychological Medicine. 2006; 36:1613–1624. [PubMed: 16882357]

Ladouceur CD, Diwadkar VA, White R, Bass J, Birmaher B, Axelson DA, Phillips ML. Fronto-limbic function in unaffected offspring at familial risk for bipolar disorder during an emotional working memory paradigm. Developmental Cognitive Neuroscience. 2013; 5:185–196. [PubMed: 23590840]

McDermott JM, Perez-Edgar K, Fox NA. Variations of the flanker paradigm: assessing selective attention in young children. Behavior research methods. 2007; 39:62–70. [PubMed: 17552472]

Nigg JT, Blaskey LG, Stawicki JA, Sachek J. Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive subtypes. Journal of Abnormal Psychology. 2004; 113:614–625. [PubMed: 15535793]

Post RM, Weiss SR, Leverich GS, George MS, Frye M, Ketter TA. Developmental psychobiology of cyclic affective illness: Implications for early therapeutic intervention. Development and Psychopathology. 1996; 8:273–305.

Roberts G, Green MJ, Breakspear M, McCormack C, Frankland A, Wright A, Levy F, Lenroot R, Chan HN, Mitchell PB. Reduced inferior frontal gyrus activation during response inhibition to emotional stimuli in youth at high risk of bipolar disorder. Biological Psychiatry. 2013; 74:55–61. [PubMed: 23245750]

Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatrica Scandinavica. Supplementum. 2007:17–26. [PubMed: 17688459]

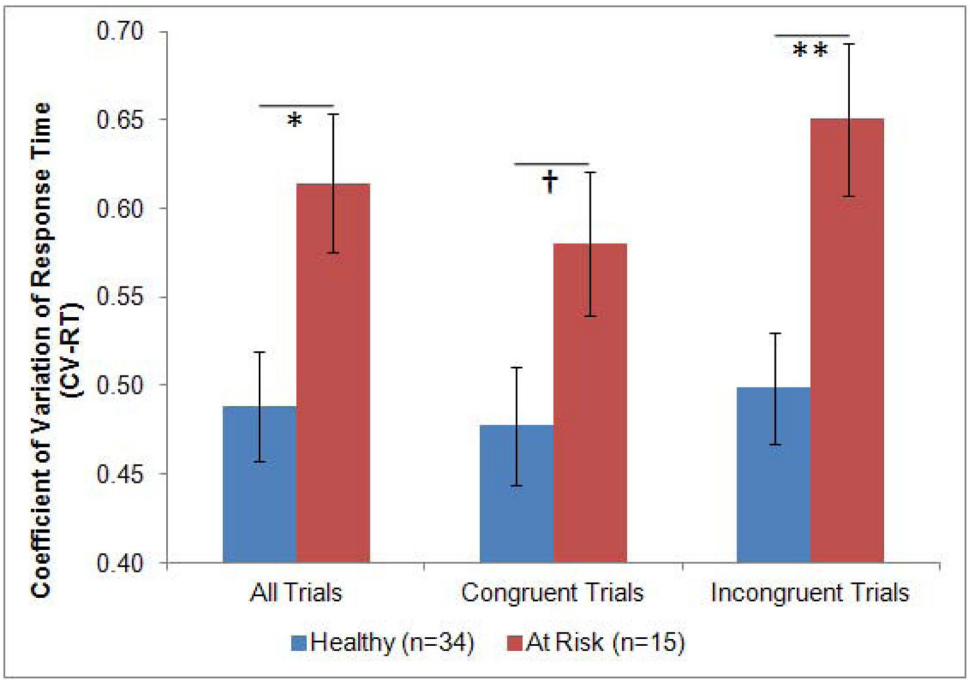

Fig 1.

Coefficient of variation of response time (CV-RT) is greater in healthy preschoolers at familial risk for bipolar disorder than low-risk healthy preschoolers for all trials, and for incongruent and congruent trials separately (** $P<0.01$,* $P<0.05$,† $P<0.1$).