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Authors

Vaughn-Coaxum, Rachel A
Merranko, John
Birmaher, Boris
et al.

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Longitudinal course of depressive symptom severity among youths with Bipolar Disorders: Moderating influences of sustained attention and history of child maltreatment

Rachel A. Vaughn-Coaxum[1], **John Merranko**[1], **Boris Birmaher**[1], **Daniel P. Dickstein**[2,3], **Danella Hafeman**[1], **Jessica C. Levenson**[1], **Fangzi Liao**[1], **Mary Kay Gill**[1], **Heather Hower**[3,4], **Benjamin I. Goldstein**[5], **Michael Strober**[6], **Neal D. Ryan**[1], **Rasim Diler**[1], **Martin B. Keller**[3], **Shirley Yen**[3,7], **Lauren Weinstock**[3], **David Axelson**[8], **Tina R. Goldstein**[1]

[1]University of Pittsburgh, School of Medicine

[2]McLean Hospital, Harvard Medical School

[3]Brown University, Warren Alpert Medical School

[4]University of California at San Diego, School of Medicine

[5]University of Toronto, Sunnybrook Health Sciences Center

[6]University of California at Los Angeles, David Geffen School of Medicine

[7]Harvard Medical School, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center

[8]Ohio State University, Nationwide Children's Hospital

Abstract

Background: Pediatric bipolar disorders are often characterized by disruptions in cognitive functioning, and exposure to child maltreatment (e.g., physical and sexual abuse) is associated with a significantly poorer course of illness. Although clinical and developmental research has shown maltreatment to be robustly associated with poorer cognitive functioning, it is unclear whether maltreatment and cognitive function jointly influence the clinical course of bipolar symptoms.

Corresponding Author: Rachel A. Vaughn-Coaxum, University of Pittsburgh, Department of Psychiatry, 557 Bellefield Towers, Pittsburgh, PA 15213, coaxumra@upmc.edu, 412-246-5058.

Methods: This secondary analysis examined moderating effects of lifetime childhood physical and sexual abuse, and cognitive disruptions (sustained attention, affective information processing), on longitudinal ratings of depression symptom severity in youths from the Course and Outcome of Bipolar Youth (COBY) study, examined from intake (M=12.24 years) through age 22 (N=198; 43.9% female; Mean age of bipolar onset = 8.85 years).

Results: A significant moderating effect was detected for sustained attention and maltreatment history. In the context of lower sustained attention, maltreatment exposure was associated with higher depression symptom severity during childhood, but not late adolescence. There was no association between maltreatment and symptom severity in the context of higher sustained attention, and no association between attention and depression symptom severity for non-maltreated youths.

Limitations: Depression symptom ratings at each assessment were subject to retrospective recall bias despite the longitudinal design. Cognitive assessments were administered at different ages across youths.

Conclusions: Depressive symptoms in pediatric bipolar may be jointly moderated by impairments in attention and exposure to maltreatment. Assessment of these risks, particularly in childhood, may be beneficial for considering risk of recurrence or chronicity of depressive symptoms.

Keywords

childhood adversity; cognitive function; depression; bipolar disorder; physical abuse, sexual abuse

The significance of neurocognitive impairments in mood disorders among children and adolescents (herein, youths) has been well-documented (Dickstein et al., 2010; Frías, Palma, & Farriols, 2014; Pavuluri, West, Hill, Jindal, & Sweeney, 2009; Wagner, Müller, Helmreich, Huss, & Tadi, 2014). In Bipolar Spectrum Disorders (BP) in particular, patterns of poorer cognitive functioning are evident among youths and adults—regardless of the presence of a mood episode or periods of euthymia. Disruptions in cognitive functioning may underly cognitive biases and inflexibility in mood pathology, and are associated with aberrant affect generation related to mood dysregulation and information processing biases in BP (Green, Cahill, & Malhi, 2007). Among specific domains of cognitive disruptions characterized in prior studies (e.g., global executive functioning, working and verbal memory, processing speed; Bourne et al., 2013; Glahn et al., 2005; Martínez-Arán et al., 2004; Torres, Boudreau, & Yatham, 2007), disrupted attention processes are commonly identified (Clark, Iversen, & Goodwin, 2002; Dickstein et al., 2004; Doyle et al., 2005; Joseph, Frazier, Youngstrom, & Soares, 2008). The salience of attention systems in BP is not surprising (see for exception Henin et al., 2007; Robertson, Kutcher, & Lagace, 2003), as attention processes underlie functioning in adjacent cognitive systems including executive functioning and memory (Lima, Peckham, & Johnson, 2018).

Cognitive and Environmental Influences on the Clinical Course of BP

Despite the robust nature of associations between cognitive disruptions and psychopathology, the influence of these disruptions on the etiology and course of BP may

not be fully understood when examined independently. Research consistently shows that environmental risk factors significantly impact youths' cognitive development and risk for psychopathology. Specifically, theoretical and empirical research supports a framework whereby childhood adversity (i.e., environmental experiences that pose a risk of harm to youths' integrity or well-being; McLaughlin, DeCross, Jovanovic, & Tottenham, 2019), is associated with disruptions in cognition—and both adverse experiences and cognitive disruptions (e.g., deficits in executive functioning, memory, attention, and atypical fear and reward processing), are linked to the development and course of psychopathology (Danese et al., 2017; McLaughlin, Sheridan, & Lambert, 2014; Miller et al., 2018; Sheridan et al., 2018).

In particular, separate lines of research have linked adversities such as childhood maltreatment (including physical and sexual abuse) with disruptions in the same cognitive systems (e.g., attention) that are commonly observed in pediatric BP (Loman et al., 2013; Pine et al., 2005; Weissman et al., 2019). Further, exposure to childhood maltreatment is associated with earlier onset BP, more mood episodes, more severe mood symptoms, higher suicidality, higher rates of comorbid posttraumatic stress disorder (PTSD), anxiety, and substance use, and more frequent psychosocial stressors (Agnew-Blais & Danese, 2016; Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011; Leverich et al., 2002; Palmier-Claus, Berry, Bucci, Mansell, & Varese, 2016; Post et al., 2015). Individuals with BP who have been exposed to childhood maltreatment may experience a more severe course, with longer duration, than individuals with BP who have never been exposed. Taken together with the evidence that cognitive disruptions contribute to difficulties with mood regulation and information processing, both factors warrant consideration for significant influence on BP outcomes.

Intersection of Cognitive Functioning and Exposure to Childhood Maltreatment

Prior research demonstrating associations between cognitive disruptions and BP, and prior evidence associating maltreatment exposure with BP, have been generated by distinct fields of study. Thus, is it unclear whether, and if so, how, cognitive disruptions and exposure to maltreatment intersect in the context of pediatric BP. Exploring joint influences of both factors on the course of BP is an important step in understanding clinical outcomes. There is some evidence that sexual and physical abuse are not directly associated with youths' cognitive functioning trajectories in pediatric BP (Frías et al., 2017). This finding is in contrast with a robust literature demonstrating direct links between maltreatment and cognitive disruptions in general (Danese et al., 2017; Mueller et al., 2010; Stuart, Hinchcliffe, & Robinson, 2019; Weissman et al., 2019). It is noteworthy, however, that prior research has focused on cognitive disruptions and maltreatment as etiological pathways to the development of BP, but there has been less focus on how these two factors shape the ongoing clinical course of BP once it emerges.

One hypothesis is that cognitive disruptions and exposure to maltreatment play a different role in the course of BP than in the etiology of BP. Specifically, if there is overlap in how

cognitive disruptions and maltreatment exposure influence BP symptoms and the capacity for mood regulation, the two factors may interact to exacerbate (or moderate) the clinical course of BP over time. As an example, maltreatment exposure is associated with cognitive disruptions in associative learning (Hanson et al., 2017; Harms, Shannon Bowen, Hanson, & Pollak, 2018), a key set of processes for learning to regulate mood that are strongly influenced by disruptions in attention processes (Pollak, 2015). In the course of BP, both maltreatment and these cognitive systems may contribute to greater impediments in emotion and mood regulation that are critical for effective symptom management. These hypothesized associations may be particularly salient for depressive symptoms, given the overlap in cognitive disruptions observed in both youth with BP and unipolar depression (Arnsten & Rubia, 2012; Wagner, Müller, Helmreich, Huss, & Tadi , 2015), and similarly strong associations between maltreatment and unipolar depression (Nanni, Uher, & Danese, 2012; Teicher & Samson, 2013).

Current Study

The primary objective of the present study is to explore how childhood maltreatment history and cognitive disruptions influence Bipolar depressive symptoms over time. To date, there is still a paucity of information on how the presence of these two types of risk influence the clinical course of youth BP. An existing prospective study that is well-suited for this investigation is the longitudinal Course and Outcome of Bipolar Youth (COBY) study. This multi-site study followed youths with BP over an average of 9.25 years (SD=2.51; range=3.46–13.66 years) with a median of 13 clinical assessments. Prior research from the COBY study identified two domains of cognitive disruption in youths with BP compared to typically developing peers. Through an assessment of multiple cognitive systems, COBY youths demonstrated disruptions in sustained attention and affective information processing (Dickstein et al., 2016). As the present study was aimed at testing moderating effects of *disruptions* in cognitive function, we focused our hypotheses specifically on these domains.

Poorer sustained attention, observed in youths and adults with BP (Doyle et al., 2005; Torres et al., 2007), is a core component of information processing and underlies additional attentional processes such as shifting and filtering, and general cognitive abilities (Sarter, Givens, & Bruno, 2001). There is also evidence of affective information processing biases in youths and adults with BP (Bauer et al., 2015; Wu et al., 2016). The two separate processes may have interrelated effects on BP pathology; disruptions in sustained attention and affective information processing may together undermine individuals' efforts to self-regulate mood and behavioral responses, particularly in the context of depressed mood (De Raedt & Koster, 2010; Joormann & Stanton, 2016; Pruessner, Barnow, & Holt, 2020). These effects may persist, as research shows that cognitive functioning among COBY youths is stable over time (Frías et al., 2017), consistent with meta-analytic findings (Frías et al., 2014; Samamé, Martino, & Strejilevich, 2014).

We hypothesized that both sustained attention and affective information processing biases would distinctly interact with history of childhood maltreatment, in association with more severe depressive symptoms over time. Specifically, we anticipated that youths with a history of childhood maltreatment would experience higher symptom severity in the context

of lower sustained attention, or greater biases toward processing negative affective information. To increase specificity in our hypothesis testing, we accounted for psychosocial and psychiatric covariates that are also associated with the proposed moderators: comorbid Attention Deficit Hyperactivity Disorder (ADHD), age of BP onset, family socioeconomic status (SES), sex, and general intelligence (IQ). As the attentional processes involved in both sustained attention and affective information processing continue to develop across adolescence and into emerging adulthood (Fortenbaugh et al., 2015; McAvinue et al., 2012; Thillay et al., 2015) we examined youths' depressive symptom severity through age 22—to better capture symptom course across the developmental progression of the cognitive processes of interest.

Method

Participants

The methods and procedures for recruitment and intake, and the full sample description for the COBY study have been extensively reported elsewhere (Birmaher et al., 2006, 2009). Briefly, inclusion criteria for a diagnosis of BP-I, BP-II, or an operationally defined BP not otherwise specified (BPS-NOS; (Axelson et al., 2006)) that is described in detail in the Supplemental Methods, were based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; American Psychiatric Association [APA], 2004). Diagnoses were assessed via the Kiddie Schedule for Affective Disorders Lifetime and Present version (KSADS-P/L; Kaufman et al., 1997). For the current study, inclusion criteria were completion of at least one Cambridge Neuropsychological Testing Automated Battery (CANTAB; Cambridge Cognition, 2006) by 22 years of age (mean age of first CANTAB = 16.66 years, SD = 3.82), no illicit substance use in the 24 hours prior to assessment, and a general IQ score of 70 or greater as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI) prior to each CANTAB.

Exclusion criteria for the full study included diagnoses of schizophrenia, intellectual disability, Autism Spectrum Disorders, and mood disorders secondary to use of substances, medications, or medical conditions. The final sub-sample included 198 youths. A total of 55.6% of these participants were diagnosed with BP-I, 10.1% with BP-II, and 34.3% with COBY-operationalized BP-NOS. The average age at intake was 12.24 years of age (SD=3.23, range = 7–17 years). See Table 1 for detailed sample demographics.

Procedures

The Institutional Review Board for each study site reviewed and approved the study protocol and informed consent and assent were obtained from the participants and parents at intake. A timeline of study procedures is presented in Figure 1. The COBY research staff administered clinical assessments to youth participants and parents in a semi-structured interview format, with an average of 7.2 months between follow-up assessments. Assessments were reviewed with a team of study investigators (psychiatrists and psychologists), who were ultimately responsible for the clinical ratings and diagnoses. As reported in prior studies, the CANTAB was introduced during the second funding cycle of the COBY study, and 53 months (on average) after the start of enrollment (Dickstein et al.,

2016; Frías et al., 2017). Cognitive assessments were administered at alternating follow-up visits to allow for at least 12 months between assessments. Participants completed a minimum of one and up to six CANTABs with a median of 15 months between assessments.

Measures

Clinical Instruments—All psychiatric diagnoses at intake were evaluated using the KSADS-P/L (Kaufman et al., 1997). The severity of mood symptoms was evaluated at intake and each follow-up assessment with the 12-item KSADS Depression Rating Scale (DRS; Kaufman et al., 1997). The DRS items are meant to determine symptom severity during a period of time prescribed by the study (usually a 1-week period); the COBY study investigators chose to focus on the most severe week in the month prior to each assessment. The Intraclass Correlation Coefficients (ICC) for the DRS interrater reliability were 0.95 or higher. The DRS was also used to assess mood symptoms in the two days prior to CANTAB completion—with no indication that symptoms were associated with performance (Dickstein et al., 2016; Frías et al., 2017).

New onset comorbid psychiatric disorders were evaluated at each follow-up assessment using the Longitudinal Interval Follow-up Evaluation (LIFE) interview Psychiatric Status Ratings (PSR) (Keller, 1987), which are linked to DSM-IV criteria (APA, 2004). At each interview, there is a retrospective recall of weekly symptomatology from the previous interview to the current interview for each diagnosis, utilizing a calendar and several memory aids. Weekly medication use (stimulants, antidepressants, lithium or other anticonvulsive drugs) was also assessed across each follow-up period. See Supplemental Methods for more detail on medication assessment and reliability statistics of PSR ratings and KSADS diagnoses.

Participants' history of childhood maltreatment (defined in the current study as physical or sexual abuse occurring prior to age 18) was assessed at intake and each follow-up using multiple measures. At intake, participants completed a medical history questionnaire and a traumatic event screening questionnaire from the KSADS PTSD section that explicitly asked about exposure to physical or sexual abuse. The Life Events Checklist (LEC; Johnson & McCutcheon, 1980), assessing negative life events (e.g., death of parent, serious illness/ injury, incarceration) in the year prior to intake, was also administered with a single question assessing any additional negative life events that were not included in the checklist. This question was used as another source to capture sexual or physical abuse. At each follow-up, new onset maltreatment was assessed based on the traumatic event screener from the KSADS and the LEC item. Lifetime history of childhood maltreatment was operationalized as endorsement of physical or sexual abuse on any one of these measures at intake or any follow-up assessment.

Finally, family SES was assessed using the Hollingshead's four-factor scale (Hollingshead, 1982) at intake, and at each follow-up assessment.

Cognitive Assessments—The CANTAB suite is one of the most widely used and extensively validated neuropsychological tests of multiple domains of cognitive function (Cambridge Cognition, 2006). For the present analysis, we included only the CANTAB sub-

tests on which youths from COBY had previously shown poorer performance compared to typically developing peers (Dickstein et al., 2016). Given prior COBY research demonstrating stability of CANTAB scores over time (Frías et al., 2017), scores on each subtest were averaged within-person to create a single score for each individual (on each performance index) across each participant's total number of assessments (range=1–6, mean=2.09). Prior to averaging the CANTAB scores, raw scores for each sub-test were z-scored based on normative data provided by Cambridge Cognition. The z-scores were used in calculations of individual person-mean scores.

Rapid Visual Processing (RVP) Task.: The RVP assesses sustained attention, and is analogous to the well-known Continuous Performance Test. A white box appears on the screen and a series of numbers (digits 2–9) appear in the middle of the box in a pseudo-random order at a rate of 100 digits per minute. Participants are instructed to hit a button when they detect a target sequence of numbers (e.g., every time they see the sequence "2–5-9"). The target sequence varies in difficulty from one to three digits. Outcome measures in the present analysis included total hits (accuracy), total misses (errors), and A′, a signal detection theory measure of sensitivity to errors, regardless of error tendency (i.e., how good the participant is at detecting the target sequence (range 0.00–1.00)].

Affective Go/No-Go (AGN) Task.: The AGN assesses information processing for negative and positive valence words. Across several blocks, a series of words is presented from two of three affective categories: (1) positive (e.g., joyful), (2) negative (e.g., hopeless), and (3) neutral (e.g., element). Participants are instructed to press a button (go) when they view a word that matches the target category (e.g., the word "happy" appears when the category is positive words), and withhold a response (no-go) when they view a word that does not match the target category (e.g., the word "despair" in the category of positive words). Outcome measures include commission errors (incorrect response to a distractor), omission errors (incorrect response to a target), and latency (milliseconds) to a correct response.

Data Analytic Strategy

Primary analyses were performed using mixed effects regression models in the "nlme" package for the R statistical software environment (version 3.6.1). A separate model was specified for each of the six CANTAB indices (three RVP, three AGN). The repeated measures total DRS scores across follow-up were regressed onto time (participant age), each CANTAB score (one index per model), maltreatment exposure, and covariates (comorbid ADHD diagnosis and medication use from the LIFE interview, age of BP onset, family SES, sex, IQ). Across all models, main effects were evaluated and the primary predictor was a three-way interaction term between each CANTAB within-person average score (fixed Level 2 variable), maltreatment history (fixed Level 2 variable), and participant age (time-varying, Level 1 variable). Observations were nested within subject. In each model non-linear effects of time were examined by adding a quadratic effect (squaring the age variable) given prior research from the COBY study demonstrating that youths tend to spend more time euthymic as they move toward adulthood (Birmaher et al., 2014). A base model with fixed effects was compared to iterative models adding a random intercept (subject) and a random slope (age) one at a time. Likelihood ratio tests were used to evaluate improvements in model fit with

each random effect. A continuous time first-order autoregressive covariance structure was specified to account for correlations between timepoints and variable numbers of months between each participant's assessments. Finally, given that three models were fit with different independent variables for the RVP task (accuracy, errors, error sensitivity) and AGN task (commission errors, omission errors, latency to correct response) two family-wise Bonferroni corrections were implemented. The *p*-value threshold was set at 0.017 (0.05/3 tests per family of cognitive indices).

Results

Demographic and Clinical Characteristics

Across primary variables, less than 1% of data were missing. Of the 211 youths who completed one or more CANTAB assessments, 11 participants were excluded for not having completed a CANTAB assessment by age 22, and an additional two participants were excluded for having mean IQ scores below 70. Demographic and clinical characteristics of the sample are provided in Table 1, and few differences were identified when comparing maltreated and non-maltreated youths using independent samples t-tests and chi-square statistics. The notable exceptions were that youths with a history of maltreatment had a higher rate of lifetime comorbid PTSD diagnoses (35.7% vs. 12.7%), and higher prevalence of ADHD (80.4% vs. 62.7%) than youths without a history of maltreatment, as well as an earlier average age of BP onset for maltreated (M=7.86 years, SD=3.05) compared to non-maltreated youths (M=9.25 years, SD=3.93), $t(196)$=2.67 p=.009. No group differences emerged for the remaining covariates selected a priori (medication use, family SES, sex, and IQ).

Primary Analyses

Tables 2–3 provide primary results for the six total mixed effect regression models, and Supplemental Tables 1–2 provide expanded results with estimates for all covariates. The best fitting model included a random intercept for individual participant, and a random slope for age at each follow-up assessment. There was significant variance in intercepts and slopes across participants, and the random intercepts and slopes were all significantly and positively correlated. The DRS was subjected to a square root transformation in every model to address skewness in the residuals.

Across all models, there were no main effects of maltreatment history in relation to DRS symptom severity scores over time (Tables 2–3). Additionally, there were no main effects of RVP task performance on DRS scores (Table 2), and no main effects of AGN task performance on DRS scores (Table 3). Youths with a history of maltreatment did not differ from youths with no history of maltreatment on any indices of RVP or AGN task performance (Table 1). A series of t-tests were also performed using the LIFE PSRs to examine the proportion of time participants spent in different mood states (euthymic, with threshold depression symptoms, and with sub-threshold depression symptoms) based on maltreatment history and cognitive performance. Results indicated no differences in the amount of time in each mood state for youths with maltreatment history compared to no

maltreatment history, or for youths with lower versus higher cognitive task performance (see Supplemental Analyses for details).

Moderation by Maltreatment History and Cognitive Function—A significant three-way interaction between RVP accuracy (total hits), maltreatment history, and time (quadratic index of age) emerged in association with DRS scores, $t(2582)=2.82$, $p=.005$ (Figure 2). Among youths with a history of maltreatment, lower levels of sustained attention (fewer hits) was associated with higher symptom severity in childhood, $\beta = 0.87$, 95% CI = 0.11–1.63, and early adolescence, $\beta = 0.42$, 95% CI = 0.08–0.77, with increasing euthymia into late adolescence. Higher sustained attention (more hits) was not associated with symptom severity. For youths with no history of maltreatment, there was no association between sustained attention and depressive symptom severity. The Least Squares Means for the estimated interaction effects are presented in Table 4. The effects survived the threshold for the family-wise Bonferroni adjusted p-value correction for multiple indices of sustained attention. No other interactions were observed between maltreatment history and other indices of sustained attention: total misses, $t(2584) = -1.45$, $p = .146$, and error sensitivity, $t(2569) = 0.82$, $p = .411$. Further, the effect was specific to sustained attention; there was no evidence that any indices of AGN task performance interacted with maltreatment history or time (age of assessment).

Post-hoc Analyses

Post-hoc analyses were performed to probe the variable developmental timing of CANTAB assessments across participants, given the finding that moderating effects were specific to DRS scores at younger ages. Participants were stratified by the timing of their first CANTAB, either in childhood or early adolescence prior to age 15 (n=70), in mid-adolescence between 15 and 17.99 years of age (n=50), or late adolescence to young adulthood between 18 and 22.99 years of age (n=78). The model with the significant interaction between maltreatment history, RVP total hits, and age) was re-fit for each age-based subgroup. Consistent with the findings for the full sample, the moderating effect emerged only for the youngest subgroup. For youths with cognitive assessments that did not take place until mid-adolescence or later, cognitive performance did not interact with maltreatment history or age. This effect is also consistent with the typical developmental course of sustained attention—a one-way ANOVA revealed that the youngest subgroup of youths also had significantly poorer performance on the RVP task than youths in the older subgroups, $F(2,193)=36.3$, $p < .001$. Subgroup differences were not influenced by maltreatment history (Supplemental Table 3).

Finally, to test the robustness of the moderating effect, sensitivity analyses were conducted to account for symptom severity (collected only for youths meeting diagnostic criteria) for comorbid diagnoses of substance use disorder [SUD] and PTSD (Supplemental Table 4). When accounting for symptom severity of PTSD and SUD, the primary interaction effects remained; however, when excluding participants with a diagnosis of PTSD (19.2% of the sample) the interaction did not survive Bonferroni correction (see Supplemental Analyses and Table 4). To further probe this finding, youths with a history of maltreatment were stratified by PTSD diagnosis (yes/no) and the two groups were compared on indices of

depression symptom severity. Maltreated youths with comorbid PTSD (n=20) did not differ from maltreated youths without comorbid PTSD (n=36) with regard to average time over follow-up in a euthymic mood state (M=42% vs. M=49%, respectively), $t(54)=1.07$, $p=.288$, average time with sub-threshold depressive symptoms (M=44% vs. M=37%, respectively), $t(54)= -1.18$, $p=.243$, or average time with full-threshold depressive symptoms (M=10% vs. M=12%, respectively) $t(54)=0.41$, $p=.686$. The two groups also did not differ with regard to their highest clinician rated DRS score over follow-up (M=23.15 vs. M=21.33, respectively). However, maltreated youths with comorbid PTSD did have higher DRS scores on average (M=10.23, SD=4.78) than maltreated youths without PTSD (M=7.69, SD=3.46), $t(54)= -2.29$, $p=.026$.

Discussion

The present study examined whether cognitive disruptions (in sustained attention and affective information processing) and exposure to childhood maltreatment jointly moderated the longitudinal severity of depression symptoms among youths with BP. Though prior research indicates that youths' mood symptoms tend to stabilize moving into adulthood (Birmaher et al., 2014), identifying factors that exacerbate symptom severity earlier in development is important, as mood episodes during youth development relate to adult functioning and psychosocial outcomes (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003; McLeod, Horwood, & Fergusson, 2016). Results suggest that specific aspects of lower sustained attention (i.e., accuracy in correctly identifying and responding to stimuli) and a history of childhood physical and/or sexual abuse may moderate depressive symptom severity over time. Lower average sustained attention was correlated with higher average symptom severity during childhood and early adolescence (but not late adolescence), only among youths exposed to maltreatment. The primary results suggest that the severity of depressive symptoms may be exacerbated by environmental risk and cognitive disruptions earlier in development, when maturation of attentional processes is occurring more rapidly, and coincidentally when maltreatment may portend the greatest risk for disruptions in cognitive development (Shonkoff et al., 2012).

Primary Hypotheses

Our primary hypothesis was that greater biases in affective information processing and lower sustained attention would interact with childhood maltreatment in association with greater longitudinal depressive symptom severity. We did not identify support for affective information processing as a moderator of symptom severity. While youths with BP have shown disrupted affective information processing in COBY and other studies, it is possible that the function of this disruption in BP is not what we hypothesized. These impairments may be characteristics that distinguish youths with BP from typically developing peers, or may have a stronger role in BP etiology, as opposed to moderating the course or severity of mood symptoms. There is also evidence of mixed results using the AGN task, with some studies replicating disruptions in affective information processing (Bauer et al., 2015) and others showing no association between BP and AGN performance (e.g., Seymour et al., 2015), particularly when accounting for depression (Bauer et al., 2016).

The hypothesized association between sustained attention and history of maltreatment as moderators of depressive symptom severity was partially supported, and only during earlier ages of development. Lower sustained attention in youths exposed to maltreatment was associated with depressive symptom severity ratings nearly one standard deviation higher in childhood, and half a standard deviation higher in early adolescence. This effect was detected when accounting for treatment with pharmacological medications and was unchanged when accounting for PTSD symptoms among participants with comorbid PTSD diagnoses. However, when excluding participants with PTSD via a sensitivity analysis, the moderating effect did not survive Bonferroni correction. One possible explanation for this finding is that excluding maltreated youths with PTSD served as a proxy for excluding youths with higher maltreatment severity—which was not assessed in the COBY study. This hypothesis seems reasonable given the results of the post-hoc analyses indicating higher average DRS scores for maltreated youths with PTSD than maltreated youths without PTSD. Finally, significant effects were specific to accuracy scores, which may represent a substrate of sustained attention that is more strongly associated with environmental risk and depressive symptoms. Prior research suggests that indices of accuracy and error sensitivity may be distinct processes, but are frequently collapsed (Fortenbaugh et al., 2015)..

Clinical and Developmental Considerations

It is also important to consider the timing of CANTAB assessments in interpreting study findings. Many participants were not assessed until late adolescence and post-hoc analyses revealed that the moderating effect was significant specifically for youths who completed their first CANTAB earlier in development. These results are consistent with the developmental trajectory of attentional systems, which mature through adolescence into emerging adulthood (McAvinue et al., 2012; Thillay et al., 2015). Importantly, despite the longitudinal study design the moderating effects were correlational, and no estimates of directionality are permitted.

The present analysis builds on the work of Dickstein and colleagues (2016) and Frías and colleagues (2017), suggesting that the association between poorer performance in certain components of sustained attention and the clinical course of depressive symptom severity in youth BP may be specific to the experience of other risk factors (i.e., childhood abuse). The pattern of symptom severity over time also supports the importance of identifying the developmental timing when BP depression symptoms are particularly pronounced, and when targeted treatment may be especially beneficial. Prior preliminary research suggests that attention processes in youth BP do not improve after pharmacological treatment (Lera-Miguel, Andrés-Perpiñá, Fatjó-Vilas, Fañanás, & Lázaro, 2015). Thus, different treatment planning approaches—such as combination treatments with psychotherapy—may be especially relevant for youths with poorer attention in the context of other risk exposures (e.g., maltreatment), particularly during the ages when cognitive processes are undergoing significant development.

At the same time, it is important to reiterate that neither disruptions in attention nor exposure to maltreatment independently correlated with higher severity of depressive symptoms earlier in youth development in this analysis (but see Andreu Pascual et al., 2020 for review

of the effects of traumatic events on BP episodes and recurrence in the full COBY sample). Though maltreatment and cognitive vulnerabilities are both risks for poorer clinical outcomes, the independent effects may be more pronounced in the timing of symptom onset and risk of recurrent episodes than the severity of depressive symptoms. To better understand the clinical implications of these dual risk factors, determining whether the interplay of attention, maltreatment, and depressive symptom severity predicts poorer functional outcomes (even after symptom severity decreases in late adolescence) is a useful future direction. It would be clinically meaningful to determine whether higher symptom severity in childhood is associated with the clinical course of mood symptoms in adulthood, as well as employment stability or risk-taking behaviors, given a host of links between depression symptoms in youth and adult functional outcomes (Keenan-Miller, Hammen, & Brennan, 2007; Lewinsohn et al., 2003; McLeod et al., 2016; Yaroslavsky, Pettit, Lewinsohn, Seeley, & Roberts, 2013).

Limitations

The results of this study should be considered in the context of several limitations. First, the majority of participants were self-reported White (reflecting the general population in the metropolitan areas of each study site at the time of enrollment), and were recruited from clinical settings, which may limit the generalizability of results and miss important sociocultural differences in factors that influence the course of Bipolar depression. Second, despite efforts to obtain precise information, the data collected through the LIFE are subject to retrospective recall bias. Third, while the CANTAB is a robust neuropsychological tool, youths in the current study completed CANTABs at varied points in development due to the COBY study design. Although we were able to conduct sub-analyses based on the developmental timing of CANTAB administration, future research replicating these findings with cognition assessed at the same point in development for all participants would be optimal. Fourth, the assessment of maltreatment was limited in multiple and important ways. The assessment of abuse lacked nuanced information regarding frequency, duration, or severity of exposure. This information may have provided clarity on the results of the sensitivity analysis excluding participants with lifetime PTSD. Further, the inclusion of exposure to neglect is important in future research, as prior work indicates that neglect is associated with distinct patterns of cognitive disruptions (McLaughlin & Sheridan, 2016; Sheridan & Mclaughlin, 2014) that may have produced unmeasured confounds. Finally, while the DRS provides a granular assessment of depressive symptoms, severity was captured only for the most severe week of the month prior to assessment and may have missed more severe segments of the follow-up period. It is possible our findings would differ had we been examining symptom trajectories.

Conclusions

In conclusion, the present study provides preliminary evidence that the severity of depressive mood symptoms for younger children and adolescents with BP may be jointly moderated by specific substrates of cognitive impairments in attentional processes and exposure to environmental risks like childhood maltreatment. These youths may spend more time with higher depressive symptoms, particularly in the earlier years of diagnosis. The assessment of history of maltreatment and cognitive functioning, particularly at younger ages, may be

beneficial in considering the risk for recurrence of depressive mood episodes during youth development, and treatment planning for chronic or recurrent symptomatology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- For youths with a history of physical or sexual abuse, poorer sustained attention was associated with higher depression symptom severity during childhood and early adolescence

- Associations among abuse history, sustained attention, and depression symptom severity may be specific to certain substrates of attention (i.e., accuracy)

- In late adolescence and early adulthood, no differential associations between attention and depression symptom severity were detected for youths with and without a history of abuse

- Average sustained attention and affective information processing scores did not differ for youths with and without a history of lifetime child abuse

- Affective information processing was not associated with history of abuse nor depression symptom severity over time
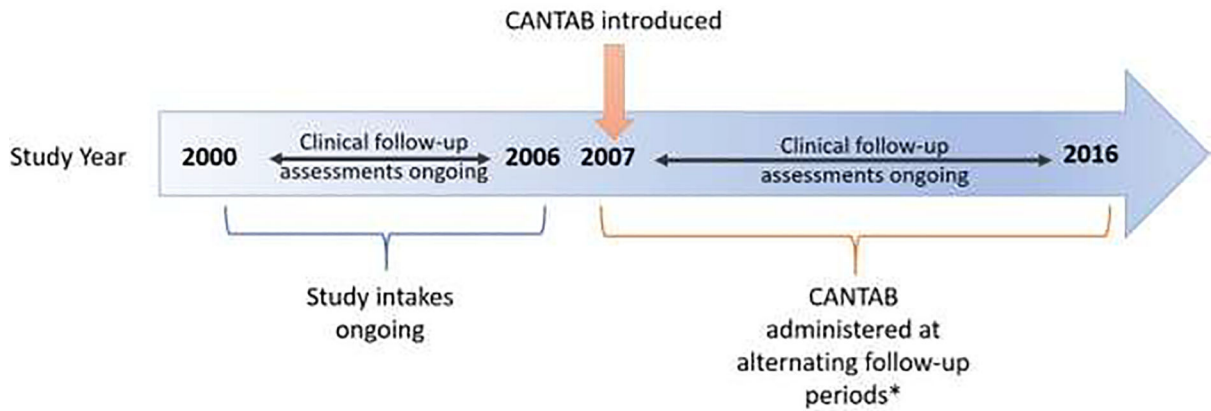
Figure 1. Timeline of Study Assessments for the Original COBY Study.
CANTAB = Cambridge Neuropsychological Testing Automated Battery. *Participants continuing to complete follow-up assessments through 2016 completed CANTABs at alternating follow-up visits to allow for at least 12 months between cognitive assessments. All study activities for participants in the current sample occurred between the years 2000 and 2016. Study intakes took place between 2000 and 2006, and clinical follow-up assessments with semi-structured interviews took place an average of every 7.2 months between 2000 and 2016. The second funding cycle for the COBY study began in 2007 and the CANTAB was introduced at that time. Participants completed a minimum of one and maximum of six CANTABs from 2007 to 2016.
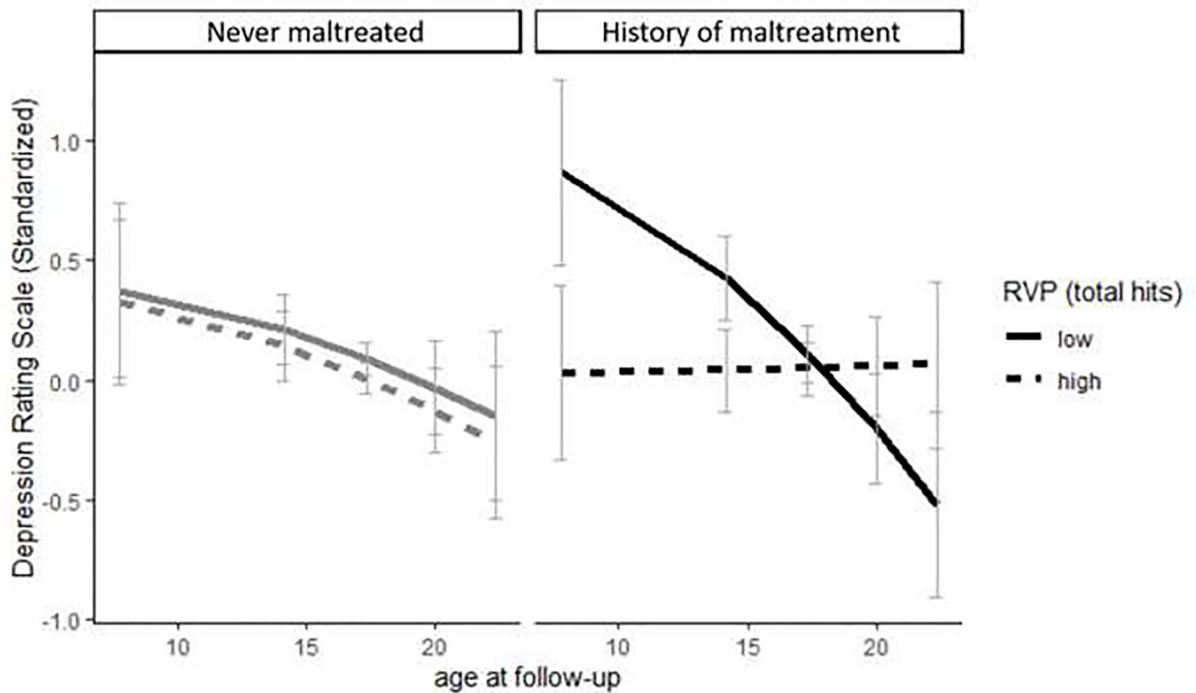
Figure 2. Severity of Depressive Symptoms over Follow-Up Moderated by Child Maltreatment History and Sustained Attention.
RVP=Rapid Visual Processing Test for sustained attention subtest of the CANTAB=Cambridge Neuropsychological Test Automated Battery. Severity of depressive symptoms over follow-up moderated by childhood maltreatment history (left vs. right panels) and sustained attention (indexed by total hits on the RVP task). Depression rating scale scores on the y-axis are standardized to illustrate differences (in standard deviations) in symptom severity from the mean score of 0. Slopes for low and high RVP scores in the left panel (Never maltreated) are non-significant. The slope for high RVP scores in the right panel (History of maltreatment) is non-significant. Only the slope for low RVP scores in the right panel represents a significant association between attention and depressive symptoms (p=.005).

Table 1.

Demographics and Clinical Characteristics

	Total Sample (N=198)	Never Maltreated (n=142)	History of Maltreatment (n=56)				95% CI	
	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)	Statistic	df	p	LL	UL
Sex				χ^2=0.04	1	.847		
Female	87 (43.9%)	63 (44.4%)	24 (42.9%)					
Male	111 (56.1%)	79 (55.6%)	32 (57.1%)					
Race				χ^2=0.17	1	.863		
White	159 (80.3%)	113 (79.6%)	46 (82.1%)					
Non-White	39 (19.7%)	29 (20.4%)	10 (17.9%)					
Family SES	3.94 (0.73)	3.97 (0.72)	3.87 (0.77)	t=0.88	196	.381	−0.13	0.33
Study Duration	9.25 (2.48)	9.22 (2.53)	9.34 (2.39)	t=−0.31	196	.757	−0.90	0.65
Age of first CANTAB	16.58 (3.82)	16.84 (3.88)	16.05 (3.64)	t=1.31	196	.191	−0.40	1.98
Age of BP onset	8.85 (3.74)	9.30 (3.92)	7.70 (2.96)	t=3.11	132.57*	**.002**	0.47	2.75
BP Diagnosis				χ^2=1.72	2	.449		
BP-I	110 (55.6%)	74 (52.1%)	36 (64.3%)					
BP-II	20 (10.1%)	17 (12.0%)	3 (5.3%)					
BP-NOS	68 (34.3%)	51 (35.9%)	17 (30.4%)					
Depression Rating Scale	8.40 (5.15)	8.32 (5.51)	8.60 (4.13)	t=−0.34	196	.732	−1.89	1.33
Lifetime Comorbidities								
PTSD	38 (19.2%)	18 (12.7%)	20 (35.7%)	χ^2=13.75	1	**<.001**		
ADHD	134 (67.7%)	89 (62.7%)	45 (80.4%)	χ^2=5.74	1	**.018**		
Any anxiety disorder	156 (78.8%)	111 (78.2%)	45 (80.4%)	χ^2=0.12	1	.734		
Psychosis	55 (27.8%)	39 (27.5%)	18 (28.6%)	χ^2=0.03	1	.876		
DBD	119 (60.1%)	79 (55.6%)	40 (71.4%)	χ^2=4.18	1	**.041**		
SUD	84 (42.4%)	55 (38.7%)	29 (51.8%)	χ^2=2.80	1	.094		
Mean IQ	106.67 (14.64)	107.70 (15.03)	104.08 (13.35)	t=1.57	196	.118	−0.92	8.15
RVP Total Hits	−0.02 (0.98)	−0.03 (1.03)	0.01 (0.85)	t=−0.13	196	.894	−0.33	0.29
RVP Total Misses	0.01 (0.98)	−0.01 (1.02)	0.07 (0.89)	t=−0.50	196	.620	−0.38	0.23
RVP A'	−0.02 (0.96)	−0.00 (0.97)	−0.04 (0.94)	t=0.27	194	.789	−0.26	0.34
AGN Commission Errors	0.04 (1.01)	−0.05 (0.98)	0.25 (1.07)	t=−1.86	195	.064	−0.61	0.02
AGN Omission Errors	0.02 (0.98)	−0.05 (0.98)	0.19 (0.97)	t=−1.54	195	.124	−0.54	0.07
AGN Latency to Correct Response	−0.02 (1.02)	0.04 (1.03)	−0.18 (0.98)	t=1.34	194	.183	−0.10	0.53

Note.

*=test adjusted for violation of Levene's Test of Homogeneity of Variance.

BP=Bipolar Disorder. CANTAB=Cambridge Neuropsychological Test Automated Battery. DBD = Disruptive Behavior Disorders (including Oppositional Defiant Disorder [ODD] and/or Conduct Disorder [CD] SUD=Substance Use Disorder (abuse/dependence). RVP=Rapid Visual Processing Test for sustained attention. AGN=Affective Go/No-Go Task. CI=Confidence Interval LL=Lower Limit. UL=Upper Limit.

Table 2

Depression Rating Scale outcomes across Rapid Visual Processing indices of sustained attention.

Predictors	Depression Rating Scale *(RVP Hits)*					Depression Rating Scale *(RVP A')*					Depression Rating Scale *(RVP Misses)*				
	β	*SE*	*CI*	*t*	*p*	*β*	*SE*	*CI*	*t*	*p*	*B*	*SE*	*CI*	*t*	*p*
(Intercept)	0.46	0.45	−0.42 – 1.34	1.02	0.307	0.05	0.04	−0.03 – 0.14	1.27	0.203	0.06	0.04	−0.03 – 0.14	1.33	0.1
Age (Quadratic)	−0.00	0.00	−0.00 – 0.00	−0.84	0.403	−0.09	0.19	−0.46 – 0.28	−0.48	0.632	−0.16	0.18	−0.51 – 0.19	−0.88	0.3
Age (linear)	0.29	0.18	−0.07 – 0.65	1.58	0.114	0.21	0.19	−0.16 – 0.58	1.10	0.271	0.30	0.18	−0.06 – 0.65	1.64	0.1
RVP (Hits)	−0.02	0.08	−0.17 – 0.13	−0.28	0.783										
Maltreatment (Abused)	0.07	0.16	−0.25 – 0.38	0.40	0.688	0.06	0.08	−0.10 – 0.21	0.69	0.489	0.05	0.08	−0.11 – 0.21	0.61	0.5
Age*RVP (Total Hits)	−0.00	0.00	−0.00 – 0.00	−0.26	0.794										
Age*Maltreatment	−0.00	0.00	−0.00 – 0.00	−0.21	0.836	−0.02	0.07	−0.15 – 0.10	−0.37	0.708	−0.02	0.07	−0.15 – 0.11	−0.35	0.7
RVP(H)*Maltreatment	−0.51	0.19	−0.87 – 0.14	−2.67	**0.008**										
Age*RVP(H)*Maltreatment	0.00	0.00	0.00 – 0.00	2.82	**0.005**										
RVP A'						−0.00	0.05	−0.10 – 0.10	−0.04	0.968					
Age*RVP(A')						−0.01	0.03	−0.08 – 0.05	−0.43	0.669					
RVP(A')*Maltreatment						0.07	0.08	−0.09 – 0.23	0.84	0.398					
Age*RVP(A')*Maltreatment						0.06	0.07	−0.08 – 0.19	0.82	0.411					
RVP Total Misses											−0.00	0.05	−0.09 – 0.08	−0.09	0.9
AGE*RVP(M)											−0.02	0.03	−0.09 – 0.04	−0.77	0.4
RVP(M)*Maltreatment											0.00	0.09	−0.17 – 0.18	0.05	0.9
Age*RVP(M)*Maltreatment											−0.11	0.07	−0.25 – 0.04	−1.45	0.1
Random Effects	σ	SD	CI	r *slope, intercept*	σ	SD	CI	r *slope, intercept*	σ	SD	CI	r *slope, intercept*			
Intercept	0.18	0.42	0.36 – 0.49	0.58	0.17	0.42	0.36 – 0.48	0.55	0.18	0.43	0.37 – 0.50	0.51			

Predictors	Depression Rating Scale *(RVP Hits)*					Depression Rating Scale *(RVP A')*					Depression Rating Scale *(RVP Misses)*				
	β	*SE*	*CI*	*t*	*p*	*β*	*SE*	*CI*	*t*	*p*	*B*	*SE*	*CI*	*t*	*p*
Slope	0.05	0.23	0.18 – 0.30		0.06	0.24	0.18 – 0.30		0.05	0.24	0.19 – 0.30				

Note. RVP = Rapid Visual Processing Task (sustained attention). BP = Bipolar Disorder. RVP(H) = RVP Total Hits; RVP(A') = RVP A'; RVP(M) = RVP Total Misses. All interaction terms with Age include the quadratic age predictor. SE = Standard Error. CI = Confidence Intervals. σ = variance. *r* = correlation.

Table 3

Depression Rating Scale outcomes across Affective Go/No-Go Task indices for affective information processing.

Predictors	Depression Rating Scale (AGN Commissions)					Depression Rating Scale (AGN Omissions)					Depression Rating Scale (AGN Mean Correct Latency)				
	B	SE	CI	t	p	β	SE	CI	t	p	β	SE	CI	t	p
(Intercept)	0.32	0.45	−0.56 – 1.19	0.71	0.479	0.30	0.44	−0.56 – 1.15	0.68	0.498	0.28	0.43	−0.56 – 1.12	0.65	0.5
Age (Quadratic)	−0.00	0.00	−0.00 – 0.00	−0.57	0.572	−0.00	0.00	−0.00 – 0.00	−0.54	0.593	−0.00	0.00	−0.00 – 0.00	−0.53	0.5
Age (Linear)	0.21	0.19	−0.16 – 0.58	1.08	0.278	0.22	0.18	−0.13 – 0.58	1.22	0.223	0.22	0.18	−0.13 – 0.58	1.24	0.2
AGN (Total Commissions)	−0.04	0.08	−0.19 – 0.11	−0.48	0.628										
Maltreatment (Abused)	0.14	0.19	−0.22 – 0.51	0.78	0.437	0.05	0.17	−0.28 – 0.37	0.29	0.770	0.11	0.16	−0.21 – 0.43	0.68	0.4
Age*AGN(C)	0.00	0.00	−0.00 – 0.00	0.07	0.942										
Age*Maltreatment	−0.00	0.00	−0.00 – 0.00	−0.35	0.729	−0.00	0.00	−0.00 – 0.00	−0.03	0.973	−0.00	0.00	−0.00 – 0.00	−0.29	0.7
AGN(C)*Maltreatment	−0.03	0.17	−0.36 – 0.30	−0.19	0.848										
AGN(C)*Age*Maltreatment	−0.00	0.00	−0.00 – 0.00	−0.11	0.910										
AGN (Total Omissions)						−0.04	0.07	−0.19 – 0.10	−0.56	0.573					
Age*AGN(O)						0.00	0.00	−0.00 – 0.00	0.52	0.606					
AGN(O)*Maltreatment						0.26	0.18	−0.10 – 0.62	1.41	0.157					
Age*AGN(O)*Maltreatment						−0.00	0.00	−0.00 – 0.00	−1.05	0.295					
AGN Mean Correct Latency											0.03	0.08	−0.12 – 0.18	0.40	0.6
Age*AGN(L)											−0.00	0.00	−0.00 – 0.00	−0.36	0.7
AGN(L)*Maltreatment											0.08	0.16	−0.25 – 0.40	0.46	0.6
Age*AGN(L)*Maltreatment											−0.00	0.00	−0.00 – 0.00	−0.59	0.5
Random Effects	σ	SD	CI	r *slope, intercept*	σ	SD	CI	r *slope, intercept*	σ	SD	CI	r *slope, intercept*			

Predictors	Depression Rating Scale (AGN Commissions)					Depression Rating Scale (AGN Omissions)					Depression Rating Scale (AGN Mean Correct Latency)				
	B	*SE*	*CI*	*t*	*p*	*β*	*SE*	*CI*	*t*	*p*	*β*	*SE*	*CI*	*t*	*p*
Intercept	0.18	0.43	0.37 – 0.49	0.55	0.18	0.43	0.37	0.55 – 0.49	0.17	0.42	0.36 – 0.48	0.55			
Slope	0.06	0.24	0.18 – 0.30		0.06	0.24	0.19 – 0.30		0.05	0.23	0.18 – 0.30				

Note. AGN = Affective Go/No-Go Task (affective information processing) BP = Bipolar Disorder. AGN(C) = AGN Total Commission Errors; AGN(O) = AGN Total Omission Errors; AGN(L) = AGN Mean Correct Latency. All interaction terms with Age include the quadratic age predictor. SE = Standard Error. CI = Confidence Intervals. σ = variance. *r* = correlation.

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Table 4.

Least Squares Means for associations between sustained attention and depression

Age at assessment	RVP Total Hits	Estimate (β)	SE	CI	
				LL	UL
No Maltreatment History					
	1 SD below mean				
7.75	−1.08	0.37	0.36	−0.33	1.08
14.14	−1.08	0.21	0.15	−0.08	0.49
17.32	−1.08	0.09	0.07	−0.04	0.22
20.00	−1.08	−0.03	0.20	−0.41	0.35
22.36	−1.08	−0.15	0.35	−0.84	0.54
	1 SD above mean				
7.75	0.88	0.33	0.34	−0.34	1.00
14.14	0.88	0.14	0.14	−0.14	0.42
17.32	0.88	0.01	0.06	−0.12	0.13
20.00	0.88	−0.13	0.18	−0.47	0.22
22.36	0.88	−0.26	0.32	−0.88	0.37
Maltreatment History					
	1 SD below mean				
7.75	−1.08	**0.87**	0.39	**0.11**	**1.63**
14.14	−1.08	**0.42**	0.18	**0.08**	**0.77**
17.32	−1.08	0.11	0.12	−0.12	0.34
20.00	−1.08	−0.21	0.23	−0.66	0.25
22.36	−1.08	−0.52	0.39	−1.28	0.23
	1 SD above mean				
7.75	0.88	0.03	0.37	−0.69	0.75
14.14	0.88	0.04	0.17	−0.30	0.38
17.32	0.88	0.05	0.11	−0.17	0.26
20.00	0.88	0.05	0.21	−0.35	0.46
22.36	0.88	0.06	0.35	−0.62	0.74

Note. RVP=Rapid Visual Processing Task (sustained attention). SE=Standard Error. CI=Confidence Intervals. LL=Lower limit. UL=Upper limit. Bold font indicates statistical significance.