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Deficient inhibitory control as an outcome of childhood trauma

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Abstract

Childhood trauma has been linked to the development and severity of psychiatric disorders, and is an environmental factor that may adversely impact executive functioning. This study investigated the performance of bipolar disorder (BD) patients and healthy controls (HC), with or without a history of childhood trauma, on a parametric go/no-go task (PGNG) measuring attention and inhibitory control. Two hundred and thirty-three individuals with BD and 90 HCs completed diagnostic interview, childhood trauma questionnaire (CTQ), symptom severity scales, and underwent a PGNG task. Four comparison groups were created using a 1.0 standard deviation cut-off of the mean of the HC total CTQ score (e.g., trauma, normative range). On the attentional task, both BD groups had significantly slower reaction time than both HC groups; however, they did not differ in accuracy. Conversely, there was a significant group difference in accuracy for the inhibitory control task, as both HC and BD trauma groups exhibited significantly poorer accuracy than HC normative. This study is one of the first to show greater dysfunction in inhibitory control in individuals with a history of trauma compared to normative groups, suggesting that early trauma might adversely impact the development of cognitive systems and brain circuits supporting executive functioning.

Keywords

Bipolar disorder; childhood trauma; stress; executive functioning; inhibitory control

Traumatic experiences, including abuse and neglect, encountered early in life are major risk factors for the development and severity of psychiatric disorders later in life (Agid, Kohn & Lerer, 2000; Caspi et al., 2003). Bipolar disorder (BD) is a severe and chronic psychiatric disorder that is associated with increased morbidity and mortality (Angst et al., 2002), including significant cognitive difficulties and associated negative impact upon everyday functioning (Ryan et al., 2013). Significant difficulties in cognitive functioning in BD have been well documented in the literature, especially in the domains of processing speed, attention, executive functioning, memory, and fine motor skills (Robinson et al., 2006; van Gorp et al., 1998). These difficulties exist even among individuals in the euthymic state

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(Thompson et al., 2005; Zubieta et al., 2001). Importantly, childhood trauma is associated with a more severe course of bipolar disorder, adversely impacting clinical characteristics such as age of illness onset, functioning, and number of mood episodes (Larsson et al., 2013; Leverich et al., 2002).

Neuroimaging has shown that childhood trauma is associated with decreased hippocampal/amygdalar volume in first episode psychosis population (Hoy et al., 2012). There are also indications that exposure to sexual abuse is related to poorer verbal and visual memory performance in BD. (Savitz et al., 2007) Not surprisingly, even in healthy populations, physical abuse and emotional neglect encountered early in life have been linked to depression, smoking and alcohol abuse, (Goldstein, Faulkner & Wekerle, 2013), deviations in negative affect understanding and cognitive control (Rogosch, Cicchetti & Aber, 1995), as well as memory and executive deficits in adulthood (Majer et al., 2010; Spann et al., 2012). Moreover, a recent study by Samplin et al. (2013) found that childhood emotional abuse correlated with higher levels of subclinical psychopathology in healthy adults, and moreover, with reduced hippocampus volume in males, but not in females. Moreover, acute stress has been implicated in the reduction of white matter in dorsolateral prefrontal cortex and this has been thought of as a potential mediating factor of executive dysfunction (Qin et al., 2009).

However, less is known about the impact of early childhood stressors on the development of executive functions and, at the brain level, development of prefrontal cortex, which is important for higher-order cognitive processes. One way to investigate executive functions is through tasks of inhibitory control. Researchers have begun to identify the differential contributions of regions typically active during tasks of inhibitory control, including right prefrontal and parietal regions (Nielson, Langenecker & Garavan, 2002), rule representation and response selection in the dorsolateral prefrontal cortex(Miller & Cohen, 2001), monitoring and error detection in the anterior cingulate cortex (Munakata et al., 2011) behavioral gating in the basal ganglia (BG) (Frank, Loughry & O'Reilly, 2001), and response inhibition in an interaction between the sub-thalamic nucleus and inferior frontal gyrus (IFG) modulated by the pre-supplementary motor area (Aron et al., 2007; Frank, 2006; Sharp et al., 2010).

While we know that executive functioning difficulties have been extensively documented in both adult and child BD (Bearden et al., 2007; Clark, Iversen & Goodwin, 2002; Frangou et al., 2005; Langenecker et al., 2010; Martinez-Aran et al., 2004), and that BD is associated with early childhood trauma (Larsson et al., 2013; Leverich et al., 2002), few studies have investigated this important relation and the impact of early childhood trauma on attention and executive functioning in BD. Moreover, to date even for the few studies trying to address this complex relationship it has been a challenge to include both patients and demographically matched healthy controls in the same study to examine the cognitive effects of trauma on executive functions. Therefore, the present study aimed to investigate the response inhibition performance of adult patients with BD (i.e., Bipolar Type I and Type II), and concurrently of a healthy control group (HC), with or without a history of childhood trauma. This study design afforded us the unique opportunity to disentangle the effects of trauma from the effects of mental illness. We focused on a task that enabled us to measure

both selective attention and inhibitory control, the Parametric Go/No-Go task (Langenecker et al., 2007b).

Based on the existing literature linking cognitive problems to early trauma in healthy population as well as BD (Majer et al., 2010; Savitz et al., 2007; Spann et al., 2012), we predicted that an early history of trauma would affect response inhibition. Moreover, based on previous studies in BD we predicted that BD would exhibit reduced inhibitory control relative to HC (Langenecker et al., 2010; Passarotti, Sweeney & Pavuluri, 2010; Ryan et al., 2013). Hence, the compounding effects of mental illness and childhood trauma in the BD group with trauma would lead to the most severe deficits in inhibitory control relative to the other three groups. Moreover, we predicted that HC with trauma would perform worse than HC/normative in terms of inhibitory control. With regard to the less challenging selective attention task with go trials we predicted that the BD groups may or may not differ from HC in accuracy or reaction time (RT).

Method

Participants

Study participants were recruited from the Prechter Bipolar Repository between October 2005 and December 2011 at the University of Michigan for a study of phenotypic and biological outcomes of bipolar disorder (for description, see Langenecker et al., 2010). Of the 586 participants recruited for the longitudinal cohort, 233 individuals with confirmed BD (191 BD Type I, 42 BD Type II) and 90 healthy controls (HC) were included in the present study. The BD and HC samples were matched on age, education, and verbal intelligence using the Wechsler Vocabulary score (Wechsler, 1999). Four comparison groups were created using a 1.0 standard deviation cut-off of the mean of the healthy controls' Childhood Trauma Questionnaire (CTQ) Total Score (M=35.76 (SD=9.60); cut-off score = 45.35). Those below the cut-off score of 45.35 were labeled normative group whereas those participants with a cut-off score equal to/or above 45.35 were labeled trauma group: BD trauma (n=117), BD normative (n=116), HC trauma (n=17), and HC normative (n=73) (Figure 1). As expected, the distribution of childhood trauma presence differed for HC and patients. Within the HC group, 81.1% did not report a history of childhood trauma compared to 18.9% with a reported history of childhood trauma. In contrast, within the BD group, 49.8% did not report a history of childhood trauma, whereas 50.2% did report a history of childhood trauma.

Recruitment of psychiatric participants occurred through an outpatient specialty psychiatry clinic, an inpatient psychiatric unit, and advertisements on the web and in the newspaper. Individuals were initially screened via telephone and those who qualified were offered an in-person baseline evaluation. All participants gave informed consent prior to participation. Participants were evaluated with Diagnostic Interview for Genetic Studies (Nurenberger, 1994; DIGS), neuropsychological testing, life event and symptom questionnaires, Hamilton Depression Rating Scale (HDRS), and Young Mania Rating Scale (YMRS). Final diagnoses were determined through a best estimate process and confirmed by at least three of the current study authors. Participants with BD were excluded from the study if they had a history of schizophrenia or schizoaffective disorder depressive type, active or current

substance dependence (within six months of baseline evaluation), or a medical illness specifically associated with depressive symptoms (including but not limited to: terminal cancers, Cushing's disease, or stroke). Those BD with active symptoms of mania or depression were excluded from this report to avoid potential for affective biases in reporting of childhood trauma. HC participants were recruited from on-line and print advertisements. HC participants were not eligible to participate if they had a history of any DSM-IV axis I disorder, active and current substance use disorder diagnosis, any medical illness specifically associated with depressive symptoms, or any first-degree family member who had been diagnosed or hospitalized for mental illness. This study was approved by the University of Michigan Institution Review Board (IRBMED: HUM00000606).

Table 1 contains demographic characteristics of the HC and BD groups. There were no significant differences between BD and HC groups for age, $F(3) = 1.41$, $p = .23$, education, $F(3) = 2.00$, $p = .11$, Wechsler Vocabulary, $F(3) = 1.91$, $p = .12$, or gender, $\chi^2(3, N = 323) = 4.462$, $p = .216$.

Clinical variables were collected during the baseline DIGS interview. Clinical variables of interest include years of illness, medication loading (Hassel et al., 2008), cumulative number of total mood episodes (including hypomania), cumulative number of episodes of mania and depression, number of hospitalizations, age of illness onset, age of first manic episode, age of first depressive episode, and length of illness. As shown in Table 1, there was a significant difference between the groups on the HDRS and YMRS, $ps < .001$, with both BD groups having higher scores than the HC groups. There was also a significant difference between the BD groups on the HDRS ($p=.001$), YMRS ($p=.046$), and total number of mania episodes (p=.014), with the BD trauma group having higher scores than the BD normative group. There was a significant difference for age at onset of first mood episode, $t(230) = 2.19$, $p = .029$, as those BD with trauma had a younger age at onset. A significant difference was also found for years of illness, $t(230) = -2.76$, p=.006, as the BD trauma group had greater years of illness compared to the BD normative group. No other differences in clinical variables were found between the BD groups.

Assessment of Childhood Trauma

All participants completed the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) which is a retrospective self-report questionnaire designed to assess five types of negative childhood experiences including emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. In clinical and community samples, the CTQ has demonstrated good internal consistency (0.63–0.95) and criterion related validity (0.50–0.75). Mean CTQ scores for each group are included in Table 1.

Assessment of selective attention and inhibitory control

The Parametric Go/No-Go task (PGNG) (Langenecker et al., 2005) (Langenecker et al., 2007a; Langenecker et al., 2007b; Votruba & Langenecker, 2013) was used to assess attention, and inhibitory control. The PGNG task requires attention, working memory, processing speed, and inhibitory control. The design was based upon an original go/no-go task developed by Garavan, Ross and Stein (Garavan, Ross & Stein, 1999), derived from the

work of Luria (Luria, 1973). Whereas the original go/no-go task consisted of two targets (i.e., the letters “x” and “y” presented among other letters of the alphabet), the PGNG has the added advantage of including three levels of increasing difficulty, with the easier first level assessing attention and the two more difficult levels (levels 2 and 3) assessing inhibitory control. Level 1 contains three targets (“x,” “y,” and “z” interspersed among other letters) and requires participants to respond by key press each time a target is presented, in order to obtain some baseline RT. Level 2 consists of two targets (“x” and “y”) and introduces a contextual inhibition component by requiring a response only when the current target is different from the previous target. Level 3 has three targets (“x,” “y,” and “z”), with the same non-repeating rule. There are a total of 1628 trials. For all levels, a serial stream of black letters (in 40-point Arial font) is presented on a white background. Each letter is presented for 500 milliseconds (ms), and there is no inter-stimulus interval. Responses within the 500ms window and for a subsequent item were considered responses to a target or lure item. This task has test-retest correlations from .73 to .83 for response time, .71 to .73 for percentage correct target trials, and .57 to .63 for percentage correct inhibition trials(Langenecker et al., 2007b).

Statistical analyses

All statistical analyses were conducted using SPSS 22. Analysis of variance (ANOVAs) and/or independent samples t-tests were used to assess between-group differences in demographic variables. Three separate ANOVAs were carried out with the 3 go/no go levels as dependent variables (DV) and the four comparison groups as independent variables (IV). A first ANOVA assessed group differences for mean attention accuracy for go/no go (levels 1–3). A second ANOVA assessed group differences for mean inhibitory control accuracy for go/no go (levels 2–3), with subsequent planned pairwise comparisons to specify the direction of the group differences. A third ANOVA assessed group differences in RT for go trials only.

Additionally, for patients only we used an independent t-test to examine possible medication effects. BD patients were taking a number of medications that varied in class and dose, which could impact cognitive functioning. Therefore, we examined the influence of medication load by using criteria based on prior literature Medications (antidepressant, anxiolytic, mood stabilizer, and antipsychotic) were coded as absent = 0, low = 1, or high = 2 in order to convert each medication to a standard dose (Almeida et al., 2009; Hassel et al., 2008; Sackeim, 2001). Antipsychotic medication was converted into chlorpromazine dose equivalents (Davis & Chen, 2004). A composite measure consisting of total medication load was then generated by summing all medication codes for each individual medication within categories for each BD participant based on Hassel’s et al. (2008) methodology.

Finally, exploratory correlations analyses were conducted to determine whether CTQ scores significantly contributed to inhibitory control accuracy for go/no go or RT for go trials.

Results

Our results showed that there was no significant group difference on go trials accuracy [$F(3, 292)=1.54$, $p=.203$] (Figure 2). However, there was a significant group difference in

inhibitory control accuracy as measured with no-go trials from levels 2 and 3 of the task [F(3, 292)=3.22, *p*=.023] (Figure 3). Pairwise comparisons showed that both trauma groups (HC and BD) exhibited significantly poorer performance than the HC normative group (*ps* <0.01). There was also a significant group effect for RT [F(3, 292)=5.214, *p*=.002] (Figure 4). Pairwise comparisons showed that both BD groups (BD normative, BD trauma) had significantly poorer performance than HC normative (*p*=.001 and *p*=.015, respectively) and HC trauma (*p*=.008 and *p*=.030, respectively), although they did not differ significantly from each other (p>.05).

With regard to medication load for patients only, there was a non-significant difference between the BD normative group and BD trauma group *t*(214)= −1.494, *p*>.05.

Importantly, exploratory correlation analyses revealed a significant inverse correlation between CTQ Total Score and mean inhibitory control accuracy (r=−1.60, p=.006). No other correlations were significant. Moreover, we found significant correlations between mean RT and illness onset age (r=.226, p=.001), age of mania onset (r=.185, p=.008), age of depression onset (r=.201), and years of illness (r=.232, p=001).

Discussion

They key finding of the current study is that both the BD and HC trauma groups exhibited significantly poorer accuracy than the HC normative group on an inhibitory control task with no-go trials. The two BD groups did not differ significantly on this inhibitory task. Moreover, there were no significant group differences in accuracy for the less challenging attention task with go trials only. These findings suggest a specific deficit in inhibitory control, but not attention in general, as a consequence of significant childhood trauma.

With regard to our participant sample we found that a history of childhood trauma is more prevalent in adults with bipolar disorder than in HC, since 50% of the BD sample, as compared to only 19% of HC, reported a history of childhood trauma. Our sample appears to be representative of the general population in that previous research shows that approximately half of adults with bipolar disorder have a severe history of childhood abuse. (Garno et al., 2005)

In support of our hypothesis, BD patients with a reported history of childhood trauma showed greater dysfunction in inhibitory control compared to the HC normative group. However, more strikingly, was the finding that the healthy control group with a history of childhood trauma also showed greater dysfunction in inhibitory control compared to the normative group. This finding suggests that early trauma may significantly detract from the development of circuits supporting inhibitory control and executive functioning, regardless of psychiatric diagnosis. Moreover, contrary to our predictions, the BD and HC groups with trauma did not differ significantly in response inhibition accuracy, which possibly suggests that the effects of early trauma may be pervasive and supersede general effects of mental illness on cognition. While physical abuse and emotional neglect early in life have been linked to memory deficits in healthy adults (Majer et al., 2010), our results extend previous findings by suggesting that early childhood trauma has an adverse impact on executive

functioning, and specifically a very important component of executive functioning, namely response inhibition, both in mentally ill BD patients and in individuals without a mental illness diagnosis. All participants in both HC groups did not meet diagnostic criteria for any mental health diagnosis at the time of baseline evaluation, although we cannot rule-out the possibility that those in the HC trauma group did not have subclinical manifestations. In this regard, a longitudinal study would be advantageous to see if any of those participants in the HC trauma group go on to develop mood disorders in the future, as well as to examine potential protective factors. As the mean age of this group is beyond the most frequent age of onset for mood disorders, it is unlikely that this reflects an independent risk factor, but an outcome. Future research could investigate what factors may have been protective for the trauma exposed HC in risk for mental illness, but not for disrupted inhibitory control.

Furthermore, our findings indicate that for the less challenging selective attentional task there were no group differences in accuracy, suggesting that the effects of mental illness and trauma may be evident only in the more cognitively challenging processes that more heavily rely on executive functions and lateral prefrontal cortex, as is the case for our inhibition task. On go trials the two BD groups had significantly slower RT relative to the two HC groups. The differences in processing speed may relate to clinical features such as effects of medications on motor speed, severity of mood symptoms, number of episodes or illness onset. For instance, exploratory correlations on clinical variables and mean RT revealed significant correlations with illness onset, onset of mania, onset of depression, and years of illness. While we found no difference in medication load within our bipolar sample, we did not parse out antipsychotic medication use, which has been found to have an effect on tasks of speeded information processing (Bearden et al., 2007)

There were also clinical and demographic features of the BD group with a history of early childhood trauma that are noteworthy in terms of functional outcome. Individuals with BD who also have a history of childhood trauma showed a more adverse course of illness compared to those BD without a history of trauma, including higher depression and mania scores, earlier age of illness onset, greater number of manic episodes, and greater years of illness. This is consistent with previous research showing that a history of early physical or sexual abuse in bipolar outpatients was associated with a higher incidence of early illness, faster cycling of frequencies and lifetime Axis I and Axis II disorders (Leverich et al., 2002). It is surprising in this context, then, that those experiencing childhood trauma and BD did not differ in executive functions relative to those without trauma experiences.

The current study has some limitations to note. Childhood trauma was assessed through retrospective recall, and we cannot measure reporting accuracy/convergent information in our participants. While there is a fundamental weakness in this type of reporting, retrospective reporting of childhood abuse has been shown to be valid and reliable in individuals with psychotic disorders (Fisher et al., 2011). Moreover, the sample of healthy controls without trauma was substantially smaller in size relative to the other three groups, and we cannot exclude that the results may have been larger, different, or more reliable if the sample sizes were more equal. Also, our study focused on attention and inhibitory control tasks, as important aspects of executive functions; but the effects of trauma and of the combined mental illness and trauma may differ in other cognitive domains such as verbal

memory, or other aspects of executive functions more related to emotional processing and emotional control.

In summary, our study is the first to demonstrate that early childhood trauma adversely impacts executive functioning which relies on prefrontal cortex, not only in patients with bipolar disorder but also in healthy individuals. Furthermore, early childhood trauma was found to contribute to a more chronic course in individuals with bipolar disorder, and in general increased risk for severe depression and substance abuse(Goldstein et al., 2013). Future studies will need to investigate what factors may curb or protect from negative long-term outcomes when trauma occurs early in life. A recent study by Goldstein et al. (2013) examined protective factors against negative outcomes in individuals who endured trauma points at internal resilience as both a compensatory and protective factor for depression symptoms in the context of sexual abuse. It is possible that cognitive processes and executive functions involved in reappraisal may contribute to strengthening internal resilience. With regard to clinical practice, our results highlight the need of routine clinical assessment of individuals at risk for early adverse experiences, as early identification, monitoring and cognitive or CBT intervention may mitigate the negative impact these adverse experiences have on the development of executive functions.

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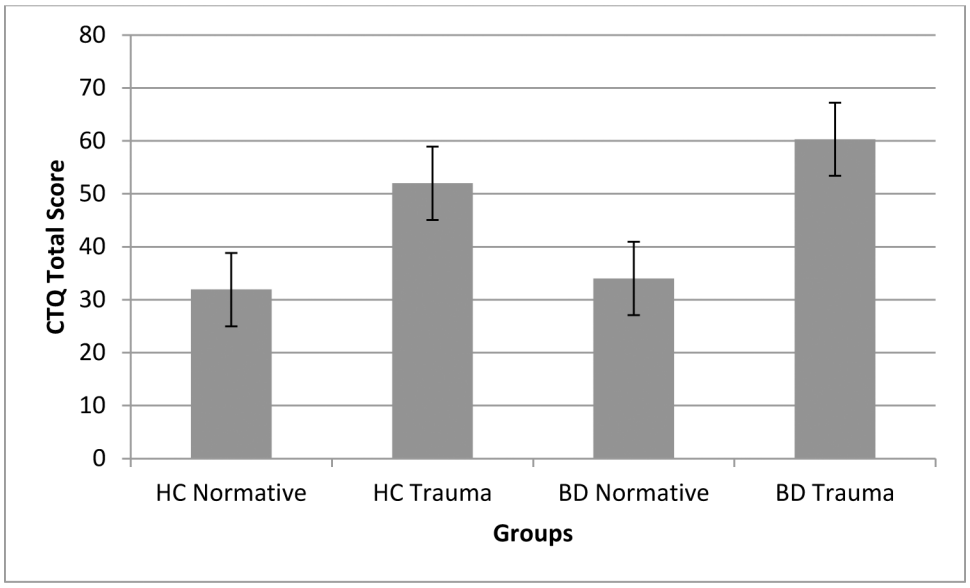

Figure 1.
Mean CTQ total score for bipolar disorder and healthy control participants.

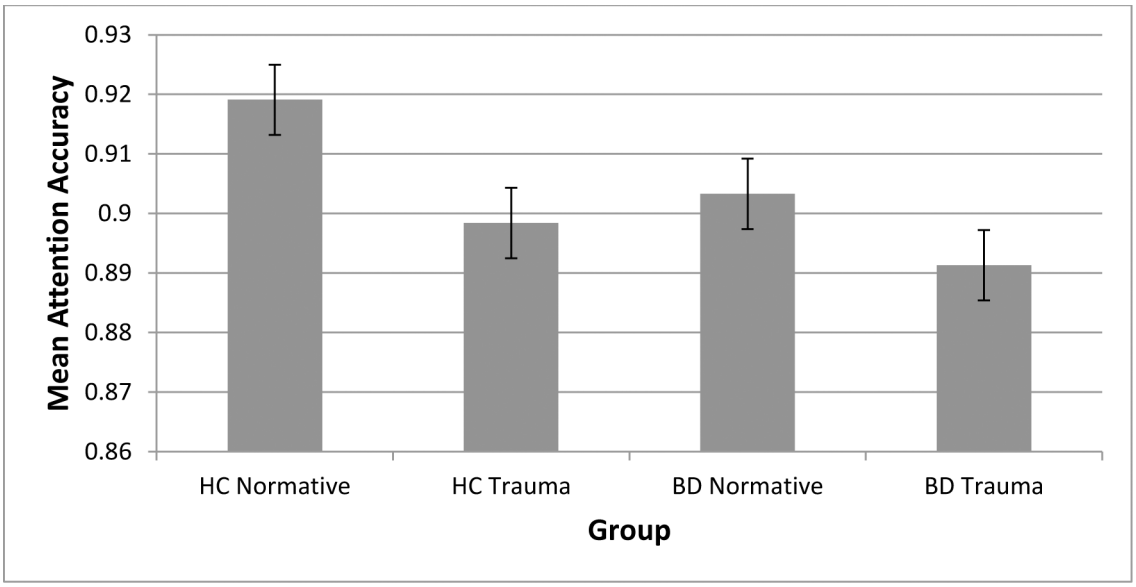

Figure 2.

Mean attention accuracy for go/no go levels 1–3 in bipolar disorder and healthy control participants with and without a history of childhood trauma.

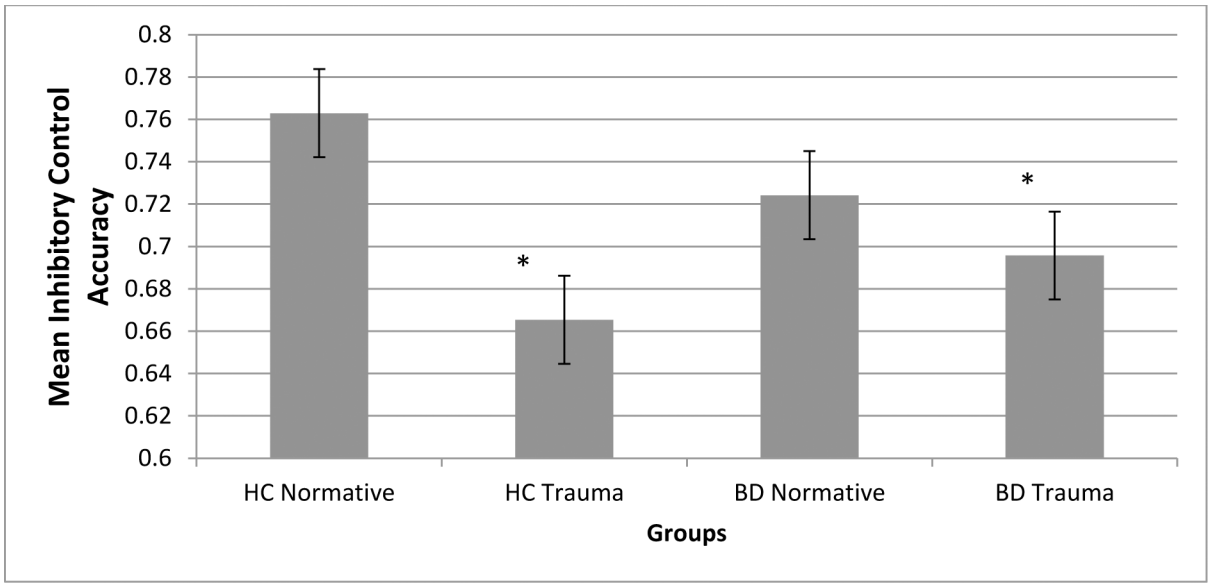

Figure 3.

Mean inhibitory control accuracy on trials in bipolar disorder and healthy control participants with and without a history of childhood trauma. * Significant difference ($p<.05$), HC Trauma and BD Trauma < HC Normative.

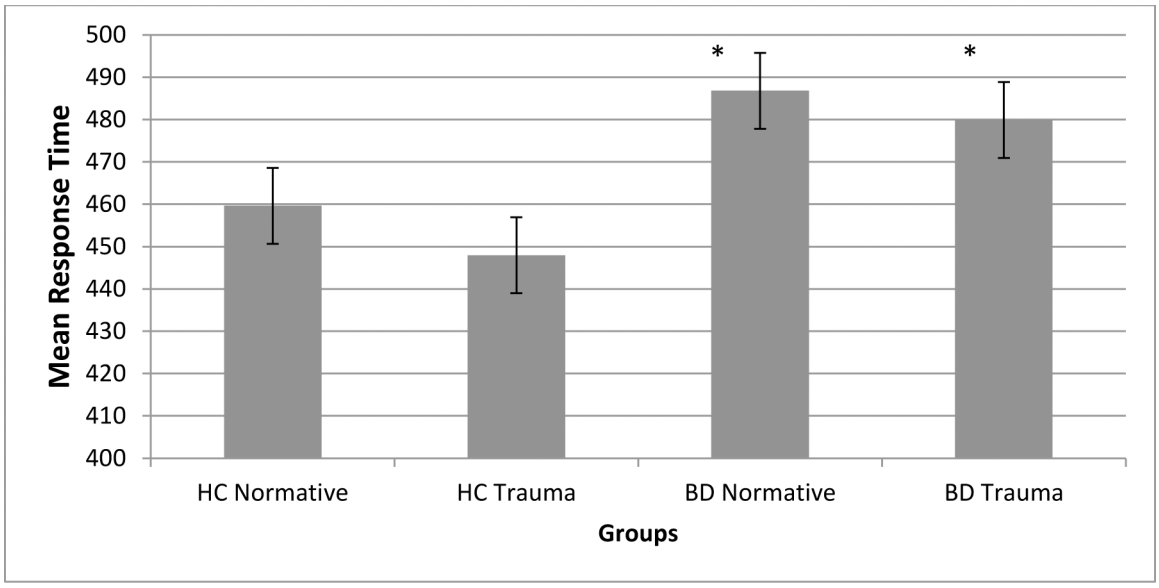

Figure 4.

Mean response time (RT) in bipolar disorder and healthy control participants with and without a history of childhood trauma. Higher scores reflect slower time. * Significant difference ($p<.05$), BD Normative and BD Trauma < HC Normative and HC Trauma.

Table 1.

Clinical and demographic characteristics in bipolar patients and healthy controls with and without a history of childhood trauma

Variable	HC Normative (n=73) M(SD)	HC Trauma (n=17) M(SD)	BD Normative (n=116) M(SD)	BD Trauma (n=117) M(SD)	p-value
Age	37.4 (14.1)	36.5 (14.2)	38.7 (13.1)	40.9 (11.4)	0.238
Education	15.9 (1.9)	15.7 (2.3)	15.7 (2.3)	15.2 (2.0)	0.113
Gender (M/F)[a]	28/45	8/9	42/74	32/85	0.216
HDRS-17	1.0 (1.4)	1.5 (1.6)	7.2 (5.6)	9.7 (5.7)	<0.001
YMRS	0.1 (0.5)	0.1 (0.3)	2.4 (3.4)	3.4 (4.0)	<0.001
WASI Vocabulary Scaled Score	12.3 (2.6)	11.9 (2.5)	12.9 (2.4)	12.2 (2.4)	0.128
CTQ Total Score	31.9 (4.6)	52.0 (8.2)	34.0 (5.5)	60.3 (14.5)	---
First Age at Onset	… …	… …	20.2 (9.3)	17.6 (8.2)	0.029
Mania Age at Onset	… …	… …	21.0 (14.0)	20.6 (12.4)	0.802
Mania Number of Episodes	… …	… …	4.7 (11.6)	10.0 (19.7)	0.014
Depression Age at Onset	… …	… …	19.6 (11.2)	18.3 (8.9)	0.340
Depression Number of Episodes	… …	… …	20.4 (48.1)	26.2 (42.2)	0.337
Hypomania Age at Onset	… …	… …	16.5 (13.0)	15.2 (12.9)	0.435
Hypomania Number of Episodes	… …	… …	22.1 (58.4)	32.7 (68.8)	0.215
Years of Illness	… …	… …	18.7 (13.1)	23.2 (11.8)	0.006
Med load	… …	… …	2.7 (1.8)	3.2 (2.3)	0.137
Number of Hospitalizations	… …	… …	4.0 (5.2)	2.9 (4.1)	0.145

[a]Chi-Square. WASI = Weschler Adult Scale of Intelligence; HDRS-17 = Hamilton Depression Rating Scale 17-item; YMRS = Young Mania Rating Scale; BD = Bipolar Disorder; HC = Healthy Control