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S100B blood levels and childhood trauma in adolescent inpatients

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Rachel Lovell did all the statistical analysis of the paper.

Barry Simon and Tatiana Falcone, did all the clinical assessments of the patients that participated in the study.

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Conflict of interest

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Abstract

Background—Serum levels of the astrocytic protein S100B have been reported to indicate disruption of the blood–brain barrier. In this study, we investigated the relationship between S100B levels and childhood trauma in a child psychiatric inpatient unit.

Method—Levels of S100B were measured in a group of youth with mood disorders or psychosis with and without history of childhood trauma as well as in healthy controls. Study participants were 93 inpatient adolescents admitted with a diagnosis of psychosis (N = 67), or mood disorder (N = 26) and 22 healthy adolescents with no history of trauma or psychiatric illness. Childhood trauma was documented using the Life Events Checklist (LEC) and Adverse Child Experiences (ACE).

Results—In a multivariate regression model, suicidality scores and trauma were the only two variables which were independently related to serum S100B levels. Patients with greater levels of childhood trauma had significantly higher S100B levels even after controlling for intensity of suicidal ideation. Patients with psychotic diagnoses and mood disorders did not significantly differ in their levels of S100B. Patients exposed to childhood trauma were significantly more likely to have elevated levels of S100B ($p < .001$) than patients without trauma, and patients with trauma had significantly higher S100B levels ($p < .001$) when compared to the control group. LEC ($p = 0.046$), and BPRS-C suicidality scores ($p = 0.001$) significantly predicted S100B levels.

Conclusions—Childhood trauma can potentially affect the integrity of the blood–brain barrier as indicated by associated increased S100B levels.

Keywords

S100B; Trauma; Children; Inflammation; Biomarker; Stress; Blood-brain barrier

1. Introduction

The adverse, long term consequences of childhood trauma can severely impact the lives of children and their future adulthood (Brown and Anderson, 1991). Several studies have demonstrated that persons exposed to trauma-induced stress in early developmental years are more likely to develop mood disorders, psychotic disorders and post-traumatic stress disorders than those who were not exposed to childhood trauma (De Bellis et al., 2010; Dennison et al., 2012; Gil et al., 2009; Jumper, 1995; Morgan & Fisher, 2007). In 2009, 3 million cases of childhood trauma were reported in the US. Retrospective studies in adult samples which evaluate the rate of trauma exposure during childhood estimate the rate to be 25–45% (Brown and Anderson. 1991; Danese et al., 2008, 2007).

There is an urgent need to investigate the effect of childhood trauma on the brain. Multiple animal model studies have evaluated the role of the hypothalamic-pituitary-adrenal axis in the patho-physiology of trauma (Lyons et al., 2010a, 2010b; Lyons et al., 2007; Parker et al., 2012; Lee et al., 2014). Studies have reported how early life stress can produce

neuroendocrine alterations (Heim et al., 2010), and how limited stress early in life can potentially impact resilience (Parker et al., 2012).

Other studies have indicated that childhood trauma is associated with a number of structural brain changes, including smaller hippocampal volume (De Bellis et al., 2010; Carrion et al., 2010; Carrion et al., 2007; De Bellis et al., 2002; Tupler and De Bellis, 2006). In youth with severe posttraumatic stress symptoms (PTSS), elevated levels of cortisol have been correlated with reduced hippocampal and prefrontal cortex (PFC) volumes (Carrion et al., 2002). In an important study, Vythilingam and colleagues reported that hippocampal volume was decreased only in depressed patients with a history of childhood trauma (Vythilingam et al., 2002). Correlations between inflammation, stress and changes in the amygdala have also recently been reported (Muscatell et al., 2014).

However, the pathophysiological mechanisms underlying the development of neurobiological consequences of childhood trauma and its relationship to development of psychiatric illness have not been fully elucidated. Disruption of the hypothalamic-pituitary-adrenal (HPA) axis with subsequent cortisol induced toxicity has been proposed as one mechanism for some of the observed neuroimaging differences in this population (Bremner, 2006, 1999; Marin et al., 2007; McCrory et al., 2010). Another proposed mechanism is a trauma-induced inflammatory response which could lead to neuronal injury (Herberth et al., 2008; Miller et al., 2009).

A more recent and novel hypothesis is that brain injury could be caused by disruption of the blood–brain barrier (BBB); therefore, leading to an influx of inflammatory cells as well as toxic compounds, resulting in potential damage to several brain areas. Studies in animal models have demonstrated that stressful situations such as immobilization, forced swimming, and training in a water maze produce BBB breakdown (Sharma and Dey, 1984, 1981; Sharma and Johanson, 2007; Sharma et al., 1992, 1995). Sharma and colleagues extensively investigated the role of the BBB under stress, and concluded that specific opening of the BBB occurs under different kinds of stressful situations (Sharma and Dey, 1984, 1981; Sharma and Johanson, 2007; Sharma et al., 1992, 1995). Lewitus and colleagues have described the role of T lymphocyte infiltration at the level of the BBB, which was associated with increase of inter-cellular adhesion molecules (ICAM-1) on the BBB (Lewitus et al., 2008). ICAM-1 has also been associated with an increased migration of inflammatory cells to the BBB (Lewitus et al., 2008). A leaky BBB can permit further accumulation of inflammatory cells, producing more inflammation and altering the BBB permeability further, leading to a self-perpetuating process (Rosenberg, 2009).

In the last few years, S100B, an astrocytic protein which is mainly produced in the brain has emerged as a valid and reliable biomarker of BBB disruption (Marchi et al., 2003a, 2003b; Marchi et al., 2011). S100B levels have been shown to correlate with the presence of radiological lesions on magnetic resonance imaging (MRI) and S100B has been evaluated as a prognostic biomarker for adults and children after traumatic brain injury (Babcock et al., 2012; Bazarian, 2010; Biberthaler et al., 2001; Kanner et al., 2003; Kapural et al., 2002; Marchi et al., 2013). Even in absence of brain injury, S100B is a biomarker of BBB disruption (Marchi et al., 2003a, 2003b). Studies comparing the role of S100B in BBB

disruption (BBBD) included the negative predictive value for abnormalities seen on a CT scan (Biberthaler et al., 2001; Blyth et al., 2009), MRI (Kanner et al., 2003; Vogelbaum et al., 2005), or to measurements of albumin in cerebrospinal fluid (CSF) (Blyth et al., 2009, 2011). A multicenter study demonstrated that in patients with TBI serum levels of S100B below 0.12 ng/mL, intracerebral lesions were not seen and these patients did not require brain imaging (Undén and Romner, 2009). Other studies on TBI (n = 1560) had similar findings where levels of S100B below 0.12 ng/mL had a negative predictive value of 99.7% (Zongo et al., 2012). The role of S100B as a BBB permeability marker in humans has been tested extensively (Marchi et al., 2003a, 2003b; Blyth et al., 2009; Biberthaler et al., 2006; Biberthaler et al., 2001; Blyth et al., 2008; Bouvier, 2013; Angelov et al., 2009; Rapoport et al., 1972; Korn et al., 2005; Tomkins et al., 2001; Gerlach et al., 2006). Some studies have reported discordant views (Koh and Lee, 2014; Kleindienst et al., 2010). Our group was able to demonstrate how extra cranial sources of S100B do not affect serum levels (Pham et al., 2010).

We and others have previously shown that S100B is elevated in several psychiatric illnesses, including psychosis and depression (Falcone et al., 2009; Rothermundt et al., 2001; Lara et al., 2001; Rothermundt et al., 2004; Rothermundt et al., 2001; Rothermundt et al., 2004; Schmitt et al., 2005; Schroeter et al., 2009; Schroeter et al., 2003; Schroeter & Steiner, 2009; Sen and Belli, 2007; Falcone et al., 2010). Levels of S100B have been reported to be elevated in patients with the following: mood disorders (Schroeter et al., 2002; Schroeter et al., 2013; Schroeter et al., 2011; Machado-Vieira et al., 2002; Schroeter et al., 2014), schizophrenia (Rothermundt et al., 2004; Rothermundt et al., 2001; Rothermundt et al., 2004; Schmitt et al., 2005; Schroeter et al., 2009; Schroeter et al., 2003), epilepsy (Marchi et al., 2009; Marchi et al., 2010) head trauma (Bazarian, 2010; Biberthaler et al., 2001, 2006; Bazarian et al., 2006; Begaz et al., 2006), melanoma (Weide et al., 2013), Parkinson's (Sathe et al., 2012), and Alzheimer's (Chaves et al., 2010). Baseline studies comparing levels of S100B in healthy controls have demonstrated levels of S100B in healthy controls to be below 0.12 ng/mL (Bazarian, 2010; Biberthaler et al., 2001; Blyth et al., 2009; Blyth et al., 2011; Blyth et al., 2008; Mussack et al., 2002; Mussack et al., 2000; Guskiewicz and Register-Mihalik, 2011; Zongo et al., 2012).

In previous publications we have reported the relationship of S100B to clinical symptoms such as suicidality (Falcone et al., 2010) and psychosis in a smaller sample of children and adolescents (Falcone et al., 2013). Patients, who had suicidal ideation or behavior as measured by the BPRS-C suicidality sub-score, had increased levels of S100B (Falcone et al., 2010). In a similar study evaluating intensity and severity of suicidal ideation in adolescents as measured by the Columbia Suicide Severity Rating Scale (CSSRS), patients who were having increased intensity and severity of suicidal ideation had increased levels of S100B (Bruce et al., 2010). In a group of adolescent patients with first episode psychosis, levels of S100B and monocyte counts were elevated (Falcone et al., 2009; Bruce et al., 2010; Falcone et al., 2013).

However, none of the previous studies have investigated and controlled for the effect of childhood adverse experiences, such as severe childhood trauma, on S100B levels. In the present study in adolescents, we investigated whether S100B levels were increased in

psychiatric in-patients with a history of trauma compared to psychiatric in-patients with no history of trauma, as well as to healthy control adolescents. We hypothesized that pediatric psychiatric inpatients with childhood trauma will have increased S100B levels when compared to psychiatric inpatients with no history of trauma and to healthy adolescent controls.

2. Materials/subjects and methods

2.1. Subjects

Subjects were 67 youth with psychosis (Psychosis Not Otherwise Specified (NOS), schizophreniform or schizophrenia), 26 adolescents with mood disorders (18 patients with major depressive disorder [MDD] and 8 patients with bipolar II-depressive episode) and 22 healthy adolescents with no history of trauma or any psychiatric disorder. Adolescent patients were admitted to the child and adolescent psychiatry unit. The protocol was approved by the Cleveland Clinic Institutional Review Board (IRB). All parents or guardians of participants signed a written informed consent; youth signed an assent to participate in the study. For this study each patient was interviewed using a semi-structured template interview developed in-house which included questions to evaluate for all different diagnoses according to DSM-IV(American Psychiatric Association, 2000). Furthermore, 2 board certified child and adolescent psychiatrists evaluated the interview and agreed on the diagnosis for each patient.

Twenty-two healthy adolescent controls were recruited through public advertising. The healthy controls were included after complete description of the research, obtaining written informed consent from the parents or legal guardians, and assent from the adolescents. The sample size in this study was based on a metanalysis of the levels of S100B in patients with clinical depression and healthy controls (Schroeter et al., 2008). The power analysis suggested that less than 22 subjects were needed to study the differences between levels of S100B among groups. These numbers led to a power statistical value of >0.95 (0.986 standard, 0.977 adjusted power calculation) using the SAS institute statistical software, JMP8 (Schroeter et al., 2008). Our sample consisted of 93 patients and 22 healthy controls.

Patient inclusion criteria were: age between 7 and 18 years, inpatients with a diagnosis of a DSM-IV TR diagnosis of psychotic disorder (psychosis NOS-schizophreniform disorder, schizo-affective disorder or schizophrenia diagnosed within the 6 months prior to admission) or MDD, or bipolar affective disorder with current depressive episode.

Patient exclusion criteria included: pregnant patients, lactating patients or patients who had delivered in the last month, psychosis secondary to a known medical condition, delirium, substance-induced psychosis, patients with a history of eating disorder, patients with diagnosed malnutrition or vitamin deficiencies, patients with lifetime history of substance abuse or a positive urine toxicology on admission, mild to severe mental retardation (IQ less than 70), autism, and other chronic neurological disorders (including epilepsy, traumatic brain injury or any other major neurodegenerative disorder which is known to affect the blood-brain barrier), patients with a history of autoimmune or endocrine disorder, history of connective tissue disorder, admitted to the hospital for any other reason in the last month

or antibiotics in the last month. Also excluded were any individuals with fever, allergies, infection or current use of antibiotics in the past month as well as patients with any major medical problem diagnosed in the last 6 months (including melanoma), asthma, infection in the last month, and patients taking lithium. The inclusion criteria for the group of healthy adolescents were: ages 7–18, who gave assent and had their parents' written consent for participation. The exclusion criteria for the healthy adolescent group were: history of inflammatory conditions (rheumatoid arthritis, asthma), history of any psychiatric diagnosis, history of psychiatric diagnosis in parents or siblings, history of schizophrenia or bipolar disorder in other close relatives, history of headaches or migraines in the last month, allergies in the last month, history of epilepsy, history of melanoma, history of traumatic brain injury, history of smoking, antibiotic use in the last month, history of any major illness in the last year, pregnancy during the last year, history of substance abuse, history of any psychotropic medication in the last year, pregnancy or delivery in the last month. Nine patients in the control group were excluded from the analysis due to limited availability of some clinical data (inability to obtain their BMI [Body Mass Index] or history of headaches or head trauma in the last month).

In this study, patients with clinical depression and patients with bipolar II depressive episode were taken into the same category, since there are three metanalysis and other studies of the levels of S100B in depression and bipolar disorder-depressive episode that confirm the levels of S100B are similarly elevated in these two groups, as well as in patients with schizophrenia (Schroeter et al., 2002; Schroeter et al., 2013; Schroeter et al., 2011; Machado-Vieira et al., 2002; Schroeter & Steiner, 2009; Najjar et al., 2013).

2.2. Clinical assessments

Two child and adolescent psychiatrists interviewed each patient and family or legal guardian to obtain a formal diagnosis and to assess the severity of symptoms.

To assess trauma exposure and possible risk factors, patient medical records were reviewed, including medical and psychiatric history, psychosocial assessments, all notes from hospitalizations, Department of Children and Family Services (DCFS) reports, legal reports and past family psychiatric history, including history of abuse by the parents. During the admission to the inpatient child and adolescent psychiatric unit, a structured comprehensive assessment was conducted, which included a detailed psychiatric interview assessing for each of the major diagnoses in the DSM IV TR and questions about exposure to trauma, details of its length, chronicity and severity, as well as legal, psychiatric or emotional consequences secondary to trauma. Additionally, to quantify the severity of the trauma, the Life Event Checklist (LEC) (Gray et al., 2004) was administered to each participant. The LEC is a trauma checklist that assesses exposure to or witnessing of 17 different severe trauma scenarios (sexual abuse, exposure to natural disasters, emotional neglect, death in the family, fire or explosion, serious accident, exposure to toxic substance, physical assault, assault with a weapon, other unwanted or uncomfortable sexual experience, combat exposure, captivity, life-threatening illness, severe human suffering, sudden, violent death and serious injury). Each event on the LEC was scored on a scale of 1–3. For this study, a score of 3 is given for any events that have happened to the subject, a score of 2 for the ones

that were witnessed and 1 for the ones that the patient had learned about. The Adverse Childhood Experience (ACE) scale was also administered. This scale addresses five personal types of trauma (physical abuse, verbal abuse, physical neglect, emotional neglect and sexual abuse), and the impact of abuse on other family members (physical or emotional abuse to parents, poverty, primary family members in jail or severe mental illness) (Dube et al., 2001). To address the severity of psychopathology, all patients were administered the Brief Psychosis Rating Scale for Children (BPRS-C) (Mullins et al., 1986). To assess suicidality the anchored question from the BPRS-C was used: 1- no suicidality is present, 2- very mild (thoughts when angry, not in the last 3 months), 3- mild (occasional thoughts but none in the last month), 4- moderate thoughts (present in the last week, no plan), 5- moderately severe (recurrent thoughts present almost daily), 6- severe (current suicidal plan, patient is not contracting for safety), 7- extremely severe (patient attempted suicide within the last week). Information on medications being taken upon admission was collected from electronic medical charts to allow for inclusion in statistical analysis. Other variables collected were age, gender and BMI.

2.3. S100B levels

All patients' samples (n = 115) underwent serum analysis of S100B protein. For S100B analysis, blood samples were collected and immediately centrifuged at 1200 g for 10 min, and the super-natant serum was stored at -80°C , until the entire sample size was achieved. The S100B concentration was measured in all samples by the Sangtec 100 ELISA (Enzyme Linked Immunosorbent Assay) method (DiaSorin, Stillwater, MN) using high and low level manufacturer provided controls to ensure proper assay performance. Serum collected parallel to that for the S100B analysis was similarly stored at -80°C . The detection limit for the S100B assays was 0.01 ng/mL. After all the samples were collected, batch analysis was performed on all the samples at the same time. The intra-assay coefficient of variance of this test is 6% (Begaz et al., 2006; Heizmann, 2004).

3. Results

3.1. Differences among trauma, no trauma, and control groups

Statistical analyses were performed using SPSS (version 20) software. Analysis of Variance (ANOVA) tests showed that the three groups (trauma, no trauma, and control) differed by age ($p < .001$) and BMI ($p = .039$). A chi-square test showed a significant difference between the three groups in terms of race when all races were included, $p = .007$ (Table 1). However, subsequent analysis revealed that the significant chi-square was due to the small counts for Asians and Hispanics. Chi-square tests were not significant for Caucasians vs. African Americans ($p = .361$) or African Americans vs. Non-African Americans ($p = .340$). A chi-square test found no significant difference between the three groups by gender, $p = .482$ and diagnosis, $p = .913$ (Table 1). A chi-square test also showed significant differences among the groups by whether or not medication was being taken ($p = .044$).

Difference of means tests found no significant difference in BPRS-C scores for the trauma vs. no trauma group ($p = .137$), but significant differences in BPRS-C suicidality ($p = .002$), LEC scores ($p < .001$), and ACE scores ($p < .001$) were found for the two groups. The three

groups (trauma, no trauma, and control) significantly differed in S100B levels ($p = .001$). The trauma group had the highest mean BPRS-C suicidality, BPRS-C, LEC, S100B, and ACE scores among the three groups.

Fig. 1 illustrates that S100B levels for the trauma group were almost three times higher than S100B levels for the control group. The S100B levels for the no trauma group were higher than the control group's levels but still much lower than the trauma group's levels. Table 2.

3.2. S100B and trauma

Difference of means tests revealed that patients who were exposed to any type of childhood trauma were significantly more likely to have elevated levels of S100B ($p < .001$) when compared to patients not exposed to trauma. Patients with trauma also had significantly higher S100B levels compared to the control group ($p < .001$) (Table 3). Patients who took medication did not have significantly higher S100B scores compared those who did not take medication ($p = .278$) and those with psychosis did not have significantly higher S100B levels compared to patients with mood disorders ($p = .245$).

Fig. 2 illustrates that those with psychosis had higher S100B levels compared to those with mood disorders, but not significantly higher. The trauma group had significantly higher S100B levels than the no trauma and control groups. Patients on medication had higher S100B levels but not significant higher.

To control for various confounding factors, we ran a multivariate OLS regression of S100B (Table 4) on gender, race (African-American and Non-African American), age, BMI, medication (yes/no), diagnostic classification (patients with psychosis and patients with a mood disorder), BPRS-C suicidality score, and LEC. According to the Shapiro Wilk test, S100B was not normally distributed ($p = .000$) and had a positive skew. We undertook several analyses to correct for this. We logged S100B and also removed outliers ($n = 3$), defined as 3 standard deviations above the mean. Transforming and removing outliers did not change the results of the analysis. BPRS-suicidality and LEC remained the only significant predictors. In fact, LEC had lower p values in these analyses and BPRS-suicidality remained highly significant. Since transforming and removing outliers did not alter the findings, we decided against these modifications to be more conservative in our approach and for interpretability reasons.

We found BPRS-C suicidality to be highly significant ($p .001$). LEC was also independently significant ($p = .046$). Thus, after controlling for suicidality, there is an independent effect of trauma on S100B. All other control variables were non-significant. Thus, holding all other included variables constant, a one unit increase in the LEC score is associated with a .011 increase in S100B levels. This model explains 20.8% of the variation in S100B levels. The standardized coefficients (betas) also indicate that the BPRS-C suicidality score was the strongest predictor of S100B levels (beta = .369), followed by the LEC score (beta = .211).

Accounting for the impact of the BPRS-C suicidality score on S100B, Fig. 1 presents the adjusted means and 95% confidence intervals for the trauma and the no trauma group. The trauma group has higher S100B levels compared to the no trauma group. In fact, the lower

confidence interval (CI) for the trauma group is higher than the mean of the no trauma group.

Further analysis was carried out to explore the relationship between the specific type of trauma and the levels of S100B as there is some preliminary evidence that extreme acts of violence can potentially produce changes in the levels of this protein. Levels of S100B were higher in those patients who reported assault with a weapon ($N = 5$) ($p < .001$), or harm to someone else after the abuse ($N = 32$) ($p < .001$). We analyzed effects of multiple kinds of trauma, although a much larger number of subjects among each specific type of trauma will be needed to further explore this relationship in future studies. Other inflammatory cytokines were collected in a sub-sample of the group, but the number needed to detect enough variation in the cytokines was not achieved.

3.3. S100B and diagnosis

Patient diagnostic classification (psychotic diagnoses and mood disorders) was included as a possible control variable in a regression model of S100B and trauma, and was non-significant ($p = .278$) (Table 4). We conducted stepwise and backward regressions (results not shown). The results of the stepwise regression show that the strongest predictor of S100B levels is BPRS-Suicide. The second strongest predictor is LEC. We also conducted a backward regression. The results show that only BPRS-Suicide and LEC were significant. BMI was the weakest predictor of S100B level, followed by whether the patient was on medication. Patient diagnostic classification was also excluded from the model due to non-significance. Thus, the results imply that patient diagnostic classification and medication do not significantly predict S100B.

Additionally, chi-square tests showed that a history of trauma did not significantly predict the patient's type of psychiatric diagnosis (psychosis or mood) ($\chi^2 = .012$, $p = .913$). Thus, patient diagnostic classification does not appear to significantly affect the relationship between S100B and childhood trauma.

3.4. S100B and gender

Although in the OLS regression model gender was not significant (Table 4), we wanted to explore this relationship further. Difference of means tests revealed that males had significantly higher S100B levels than females ($p = .022$). A bivariate regression also showed gender to be a significant predictor of S100B ($p = .026$). However, when trauma was added to the regression model, trauma became highly significant ($p < .001$) and gender became nonsignificant ($p = .055$). These findings suggest that gender and S100B have a spurious relationship.

4. Discussion

The results of this study indicate that the more severe exposure patients had to childhood trauma, the higher their levels of the BBB disruption biomarker S100B. Compared to the control group, levels of S100B were elevated regardless of diagnosis, and there was no diagnostic effect when the effect of trauma was controlled. In a multiple regression model, the only two factors which were significantly and independently related to S100B levels

were the level of suicidality (as reported by us previously (Falcone et al., 2010; Bruce et al., 2010)) and childhood trauma. All other relationships with diagnosis, age, gender, BMI and others were non-significant when effects of suicidality and trauma were regressed out.

In a study comparing the levels of S100B in 39 healthy soldiers after 6 weeks of combat training vs. the same group after 12 days of resting, levels of S100B, serum cortisol, IL-6 and TNF-alpha were elevated. Authors concluded that the stress of combat training increases inflammatory mediators and propose alterations in the BBB permeability as one of the mechanisms for cognitive dysfunction under stress (Li et al., 2014). The role of peripheral immunity in regulating BBB permeability has also been reported (Bargerstock et al., 2014). The findings of our study are in accordance with previous studies in animal models, which demonstrated that chronic trauma during early development produced increased levels of S100B (Sharma and Dey, 1981; Diehl et al., 2007; Margis et al., 2004; Scaccianoce et al., 2004; Friedman et al., 1996). In animal models, Diehl demonstrated rats exposed to maternal separation in the first 10 days of life had increased levels of S100B and male rats chronically exposed to shock had persistent high levels of S100B (Diehl et al., 2007). Esposito and colleagues reported that acute restraint stress in rats increased BBB permeability mediated by mast cells (Esposito et al., 2003; Esposito et al. 2001; Esposito et al., 2002). In an attempt to elucidate the role of corticosterone in rats exposed to stress, Scaccianoce and colleagues performed an adrenalectomy and then exposed the animals to restraint stress. The rats exposed to the stress had increased levels of S100B despite having an adrenalectomy (Scaccianoce et al., 2004).

The pathophysiological mechanism of the relationship between childhood trauma and S100B is unclear at this time and can only be speculated. A potential hypothesis could be that after emotional trauma that is severe enough to trigger the peripheral inflammatory response, activated monocytes would produce cytokines that will cross the BBB leading to activation of the glial cells (Andrews and Neises, 2012). Activated microglia will also produce cytokines, perpetuate local brain inflammation and further promote the BBB breakdown (Shalev et al., 2009).

Levels of S100B were not affected by the use psychotropic medications, as reported by us and others (Rothermundt et al., 2001; Schmitt et al., 2005; Schroeter et al., 2003; Falcone et al., 2010). Evidence from metanalysis concluded that levels of S100B are elevated in patients with mood disorders and schizophrenia and that levels of S100B were not affected by psychotropic medication. (Schroeter et al., 2009; Schroeter & Steiner, 2009; Aleksovska et al., 2014).

Although the association between severity of exposure to childhood trauma and S100B, in a clinical population indicated the effect of childhood trauma on BBB damage, the absence of measurement of levels of S100B before the trauma limits our ability to understand what happens first – the effect of childhood trauma or the alteration of the BBB. Although the levels of S100B in healthy adolescent controls were below 0.12 ng/mL. Future prospective longitudinal studies are needed to investigate the role of S100B in patients with recent trauma and how the effect of emotional trauma relates to the development of brain structural and functional changes over time and whether these changes correlate with increased

incidence of neuropsychiatric illnesses (Zongo et al., 2012; Taira and Schriger, 2012; Ruan et al., 2009).

In this study we excluded patients with a history of head injury, but in patients exposed to childhood trauma, physical trauma might be underreported. In order to circumvent this issue, we reviewed all medical and emergency room visits for each one of the patients, as well as checking DCFS records on every patient to account for unreported traumatic brain injury in the patients. Patients with known traumatic brain injury were then excluded from the study. Future studies prospectively assessing levels of other in-inflammatory markers are desirable. A SCID or MINI was not used as it could not easily be incorporated in the clinical evaluation while these patients were being admitted as inpatients, a semi-structured template interview created in-house according to all the child and adolescent diagnosis in the DSM-IV was used to evaluate each patient. After the semi-structured interview by 2 child psychiatrist a consensus diagnosis meeting was held for each patient.

In conclusion, the findings of this study indicate that increased S100B levels are related to acute suicidality as well as chronic effects of childhood trauma. The implications of these findings for pathophysiology of major psychiatric illnesses need to be explored further in future studies.

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Fig. 1.

Mean S100B levels by Patient Group. The trauma group had S100B levels that were almost over three times higher than the control group. The no trauma group had S100B levels that were higher than the control group but were still much lower compared to the trauma group. No trauma group in this figure excluded healthy controls.

Fig. 2. Mean S100B Levels by Comparison Group. This figure graphically illustrates the results from Table 3. Those with psychosis had higher S100B levels compared to those with mood disorders but this difference was not significant. The trauma group had significantly higher S100B levels compared to the no trauma and control groups, respectively. (Trauma group in this figure included healthy controls.) Those patients on medication had higher S100B levels but this difference was not significant.

Table 1

Summary of demographic characteristics of the sample by type of group. In this table we have demographic and clinical characteristics of the sample. The three groups (trauma, no trauma, and control) did not significantly differ by gender or diagnosis ($p = .482$ and $.913$, respectively). The groups did have significantly different ages ($p < .001$) with the control group being the oldest. The groups also differed by race ($p = .007$), which is most likely due to the small number of Hispanics and Asians included in the study. The three groups also had significantly different BMI scores ($p = .039$) and medication use ($p = .044$).

	<u>Trauma</u>	<u>No trauma</u>	<u>Control</u>	<u>P value</u>
	<u>N = 60</u>	<u>N = 33</u>	<u>N = 22</u>	
	<u>Mean (Std.)</u>	<u>Mean (Std.)</u>	<u>Mean (Std.)</u>	
<i>Age</i>	14.20 (2.77)	15.53 (2.13)	16.59(1.01)	<.001
<i>BMI</i>	24.56 (5.44)	26.72 (5.72)	22.86 (5.14)	.039
<i>Gender</i>				.482
Female	25	17	12	
Male	35	16	10	
<i>Race</i>				.007
African American	13	10	3	
Asian	1	0	4	
Caucasian	36	18	15	
Hispanic	10	5	0	
<i>Diagnosis</i>				.913
Psychosis	43	24		
Mood Disorder	17	9		
<i>Medication</i>				.044
No	16	3		
Yes	44	30		

Table 2

Summary of clinical scales and levels of the S100B comparing the presence or absence of trauma. The three groups had significantly different BPRS-C suicidality ($p = .002$), LEC ($p < .001$), S100B ($p = .001$), and ACE ($p < .001$) scores. The Trauma group had higher BPRS-C suicidality and BPRS-C scores, LEC scores, S100B, and ACE levels. SD = standard deviation. No trauma group excluded healthy controls.

	<u>Trauma</u>	<u>No trauma</u>	<u>Control</u>	<u>P value</u>
	<u>N = 60</u>	<u>N = 33</u>	<u>N = 22</u>	
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
BPRS-C suicidality	4.90 (2.65)	3.18 (2.00)		.002
BPRS-C	65.38 (18.40)	58.88 (22.69)		.137
LEC	11.98 (5.31)	2.0 (2.29)		<.001
S100B	.313 (.35)	.146 (.12)	.106 (.09)	.001
ACE	4.0 (2.46)	2.0 (1.62)		<.001

Table 3

Summary of statistical difference tests with S100B as outcome. There were no significant differences in S100B levels between the psychosis and mood disorder groups ($p = .245$) and medication and no medication groups ($p = .278$). All other group comparisons showed significant differences in S100B levels. A negative test statistic indicates the first column had higher S100B levels. Trauma group in this table included healthy controls.

Comparison groups		Test statistic	P value
<i>Psychosis</i>	<i>Mood disorder</i>	$t = -1.17$	.245
M = .252	M = .190		
SD = .316	SD = .223		
<i>Trauma</i>	<i>No trauma</i>	$t = -3.84$	<.001
M = .313	M = .130		
SD = .353	SD = .112		
<i>Trauma</i>	<i>Control</i>	$t = -4.01$	<.001
M = .313	M = .106		
SD = .353	SD = .091		
<i>Medication</i>	<i>No medication</i>	$t = -1.09$	.278
M = .272	M = .187		
SD = .333	SD = .122		

Table 4

OLS regression of S100B on gender, race, Age, BMI, medication, psychosis diagnosis, BPRS-C suicidality and LEC. BPRS-C suicidality was highly significant. LEC was also significant after controlling for the effect of suicidality; therefore, there was an independent effect of trauma on S100B after accounting for suicidality. Those with higher BPRS-C suicidality and LEC scores had higher S100B levels. None of the other variables were significant.

	Coeff.	Std. error	Beta	P value
Constant	-.048	.259		.853
Female ^a	-.059	.061	-.097	.341
Black ^b	.085	.070	.121	.230
Age	.002	.013	.017	.879
BMI	-.005	.006	-.086	.427
Medication ^c	.085	.072	.114	.239
Psychosis Diagnosis ^d	-.077	.070	-.114	.278
BPRS-C suicidality	.047	.013	.369	.001
LEC	.011	.005	.211	.046
Adj R	.208			
N	93			

^a Male is the reference group.

^b Non-black is the reference group.

^c No medication is the reference group.

^d Mood Disorder is the reference group.