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The Impact of Childhood Trauma on the Association Between Inflammation and Negative Symptoms of Schizophrenia

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Schizophrenia is a severe and multifactorial psychiatric disorder that is characterized by a combination of positive, negative, and cognitive symptoms. Negative symptoms are strongly associated with worse functional outcomes and the immense illness burden. Because inflammatory markers are associated with negative symptoms in schizophrenia, immune system abnormalities may be one mechanism behind these symptoms. In addition to being a risk factor for schizophrenia, childhood trauma has been associated with elevated systemic inflammation in adulthood and worse negative symptoms. Considering past literature has identified a positive association between both inflammation and negative symptoms of schizophrenia as well as childhood trauma and psychopathology severity in schizophrenia populations, we hypothesized that pro-inflammatory cytokines would be positively correlated with negative symptoms as well as childhood trauma prevalence. Additionally, we hypothesized that childhood physical and emotional neglect, rather than the other childhood trauma subtypes, will be positively associated with greater negative symptoms. Fifty individuals from Grady Memorial Hospital's psychiatric outpatient clinics who met the criteria for schizophrenia or schizoaffective disorder were enrolled in the study. During enrollment, each patient completed behavioral questionnaires, was interviewed for psychiatric/medical history and demographic information, and provided blood for screening labs and assay of inflammatory markers. We found that childhood emotional and physical neglect were positively correlated with the deficits of motivated behavior domain of negative symptoms (AAA: avolition, asociality, anhedonia), as indexed by the Brief Negative Symptom Scale (BNSS). In individuals with high BNSS AAA scores, we identified positive trends for a relationship between TNF-α with childhood trauma overall, as well as emotional abuse and physical neglect. When looking at the subgroup of patients with both high BNSS AAA scores and high inflammation (as indexed by CRP), we found a positive correlation between the pro-inflammatory cytokine IL-6 with the CTQ Physical Neglect subscale. Our findings regarding childhood trauma and negative symptoms align with theoretical pathways that suggest how childhood trauma can lead to negative symptoms later in life. Considering the literature linking inflammation to negative symptoms, childhood trauma may be involved in negative symptoms via disruptions in the inflammatory response.

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Introduction

Schizophrenia

Affecting approximately 1% of the global population, schizophrenia is a severe and multifactorial psychiatric disorder that often appears in early adulthood or late adolescence (Stilo & Murray, 2010; Picchioni et. al., 2007). Schizophrenia manifests as a heterogeneous combination of positive, negative, and cognitive symptoms. Positive symptoms include exaggerated behaviors or sensations that do not normally emerge in unafflicted individuals, such as hallucinations, delusions, and anosognosia (Picchioni et. al., 2007). On the other hand, negative symptoms reflect typically present behaviors that are now reduced or absent, such as social withdrawal, anhedonia, blunted affect, and reduced motivational drive (Buchanan, 2007). According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, a diagnosis of schizophrenia or schizoaffective disorder is based on "…the persistence of two or more of the following active-phase symptoms, each lasting for a significant portion of at least a one-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms" (APA, 2013; Patel et al., 2014). To qualify for schizophrenia, at least one of the following needs to be present: delusions, hallucinations, or disorganized speech (APA, 2013; Patel et al., 2014).

Historically, negative symptoms have been described as a reduction of typical behaviors, (Liemburg et al., 2013). In 2005, the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) panel specified the following five subcategories in negative symptoms: alogia, anhedonia, asociality, avolition, and blunted affect (Kirkpatrick et al., 2006). Still, efforts have been made to continue recategorizing negative symptoms through confirmatory and exploratory analyses (Foussias and

Remington, 2010). The most current approach, which has even been posited in the most recent edition of the DSM (DSM-V), describes negative symptoms as a two-domain model in which symptoms fall into deficits in expressivity or deficits in motivated behaviors (APA, 2017). Within this model, alogia and blunted affect combine to make deficits in expressivity whereas anhedonia, asociality, and avolition comprise the deficits in motivated behaviors domain (Messinger et al., 2011).

Negative symptoms are strongly associated with poor functional outcomes and the immense illness burden of schizophrenia (Leifker et al., 2009; Harvey, 2013; Fervaha et at., 2014). Nonetheless, current psychiatric interventions, including antipsychotic medications, fail to treat these symptoms as effectively as positive symptoms (King, 1998; Abou-Setta, 2012). In fact, given the considerable side effects of both typical and atypical antipsychotics, these medications can even worsen the negative symptom profile by creating secondary negative symptoms (King, 1998). With negative symptoms being associated with impaired occupational and academic performance, diminished social functioning, as well as worse quality of life, pursuing novel approaches to their pathophysiology could lead to the development of more effective treatments for these symptoms that have been insufficiently addressed in contemporary treatments (Correll and Schooler, 2020).

Inflammation: the Role of Peripheral Cytokines

In a world full of pathogenic microbes, toxins, and allergenic compounds, organisms have had to evolve defense mechanisms for the sake of their own survival, such as the immune system. As the major line of defense against external threats, the immune system uses innate and adaptive biological mechanisms to identify and combat these harmful stimuli, while minimizing

harm to the host (Chaplain, 2010). Emerging from the immune system, inflammation is a predominant biological defense mechanism that acts by identifying and destroying harmful stimuli while minimizing damage and infection to the body (Chen et al., 2017).

Involved in the modulation of the inflammatory response, cytokines are a family of small proteins that are involved in the regulation of immune responses through their production in cell signaling cascades and interaction with cell surface receptors (Zhang et al., 2007). Predominantly released from immune cells like monocytes, macrophages, and lymphocytes, cytokines can act as pro-inflammatory or anti-inflammatory mediators in the inflammatory response (Chen et al., 2017). Including interleukin (IL)-1β, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α, pro-inflammatory cytokines activate the immune response by supporting apoptotic pathways, triggering further cytokine production through the activation of leukocyte chemotaxis, and initiating the NF-κB pathway that supports inflammation by triggering pro-inflammatory cytokine expression and recruiting inflammatory cells (Chen et al., 2017). On the other hand, anti-inflammatory markers such as IL-1, Il-4, and IL-10 regulate their pro-inflammatory counterparts through acting as receptor antagonists to pathways that would otherwise induce the expression of pro-inflammatory cytokines (Zhang, et. al., 2007).

Acute inflammatory responses involve a short-term upregulation of inflammatory activity in the presence of the host that deactivates once the biological threat has been resolved. When the acute inflammatory response becomes dysregulated as a result of socioenvironmental and biological factors, there is a higher risk for low-grade systemic chronic inflammation (SCI) (Furman et al., 2019). Systemic chronic inflammation is a driving force behind various leading causes of death worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, as well as autoimmune, neurodegenerative and psychiatric disorders (Furman et.

al., 2019). When assessing for the presence of inflammation, pro-inflammatory and anti-inflammatory markers are often measured. Though not a cytokine, c-reactive protein (CRP) is a non-specific, acute phase reactant that is synthesized in the liver in response to increased inflammation (Dickerson et al., 2013). Because CRP is often correlated with inflammatory cytokine concentration changes in both the peripheral and central nervous systems, CRP has been regarded as a reliable indicator of systemic inflammation (Felger et al., 2018).

Inflammation and Schizophrenia

As a complex psychiatric disorder that is influenced by a combination of genetic, environmental and stochastic factors, schizophrenia symptomology can be influenced by alterations in physiological organ systems outside of the nervous system (Boozalis et al., 2018). There are various hypotheses that suggest how immune system abnormalities may be increasing the risk of developing schizophrenia. Miller and Goldsmith (2020) summarize various proposed explanations, including implicated immunogenetic variations, prenatal exposure to infectious agents, as well as decreased levels of immune acute phase proteins in the neonatal period, childhood, or adolescence. With CRP and cytokines as the commonly measured markers for inflammation in clinical settings, several studies have found associations between aspects of the immune system and schizophrenia symptomology (Goldsmith et al., 2018; Lee et al., 2017; Liemburg et al., 2018; Miller et al., 2014).

One meta-analysis found increased concentrations of interleukin-1β (IL-1β), soluble IL-2 receptor (sIL-2R), IL-6, and TNF-α with significant effect sizes in medication naïve first-episode patients (Upthegrove et al., 2014). These findings align with the results reported in previous meta-analyses, such as Miller et al. (2014) and Goldsmith et al. (2016). Miller et al. (2014)

assessed studies that examined samples of first-episode psychosis (FEP) patients and acutely relapsed inpatients who have experienced an acute schizophrenia exacerbation against healthy controls whereas Goldsmith et al. (2016) included studies that examined acutely and chronically ill patients with schizophrenia. Analyzing 40 studies, Miller et al. (2014) found IL-1β, IL-6, transforming growth factor β (TGF-β), IL-12, interferon-γ (IFN-γ), TNF-α, and sIL-2R to be elevated in both FEP and acutely relapsed subjects. However, this meta-analysis also found that antipsychotic treatment normalized the concentrations of IL-1β, IL-6, TGF-β, but not IL-12, IFN-γ, TNF-α, and sIL-2R. This differential response to antipsychotic treatment suggests that some inflammatory marker abnormalities in patients with schizophrenia may be state markers while others may be trait markers independent of antipsychotic treatment. Like Miller et al. (2014), Goldsmith et al. (2016) found abnormal cytokine concentrations in their meta-analysis. Compared to the controls, Goldsmith et al. (2016) found that IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-10, sIL-2R, TGF-β, and TNF-α were elevated in the first-episode psychosis patients. Similarly, Goldsmith et al. (2016) found that the chronically ill schizophrenia group had higher concentrations of IL-1β, IL-6, sIL-2R, and TNF-α compared to healthy controls. In addition to identifying several studies finding elevated microglia density and activation during active psychosis as well as chronic macrophage activity in schizophrenia patients, one review noted a pattern of elevated pro-inflammatory cytokine and chemokine concentrations as well as lower anti-inflammatory concentrations in schizophrenia patients (Beumer et al., 2012).

Moreover, there is a growing literature centered on identifying how inflammation may be implicated in the progression and symptomology of schizophrenia (Goldsmith et al., 2018). For instance, several studies have found elevated levels of inflammatory markers like C-reactive protein (CRP) in schizophrenia patients, (Dickerson et al., 2013; Miller et al., 2014), where

greater CRP is specifically associated with more severe symptomology such as cognitive impairment (Fan, et al., 2007; Bulzacka et al., 2016), though these findings are not always consistent (Dickerson 2007). Several studies have demonstrated relationships between CRP and negative symptoms based on the Positive and Negative Symptoms Scale (PANSS; Boozalis et al. 2018 and Liemburg et al. 2018*)*. Furthermore, patients with deficit schizophrenia, characterized by predominant negative symptoms, were found to have elevated concentrations of CRP as well as the pro-inflammatory TNF-α and IL-6 compared to non-deficit patients and healthy controls (Garcia-Rizo et al., 2012; Goldsmith et al., 2018). When examining individuals at clinical high risk for psychosis, another study found that TNF predicted a worsening negative symptom trajectory independent of depression (Goldsmith et al., 2019). These studies reflect a pattern of inflammatory biomarkers playing a role in the symptomology of schizophrenia. However, it appears that these associations are not present in every person with schizophrenia, which suggests that elevated inflammation may be characteristic of a certain subtype of schizophrenia.

There has been recent interest as to whether the effects of inflammation on brain regions that mediate motivational deficits observed in patients with depression and healthy controls given exogenous inflammatory stimuli may also underlie negative schizophrenia symptomology (Goldsmith and Rapaport 2020). Briefly, individuals with depression who have evidence of increased inflammation have decreased activation of the ventral striatum, an area of the brain known to be sensitive to reward processing, as well as decreased connectivity in brain reward circuitry in association with increased anhedonia (Miller and Raison, 2016). Similarly, symptoms of motivational deficits were shown to improve in individuals with depression and high inflammation who were given the tumor necrosis factor antagonist infliximab (Raison et al., 2013). Patients with schizophrenia have motivational deficits (negative symptoms) and show

evidence of hypoactivation of the ventral striatum in response to reward anticipation (Radua et al., 2015). Whether inflammation may impact brain reward circuitry in patients with schizophrenia similar to what has been shown in depression remains unknown, though given the associations between inflammatory cytokines and negative symptoms discussed above, the hypothesis of a transdiagnostic association is intriguing.

Childhood Trauma

One potential source of chronic inflammation in patients with schizophrenia is childhood trauma. Early life experiences can have a profound impact on an individual's development, adulthood, and wellbeing. As a subset of Early Life Stress (ELS), childhood trauma is defined in the DSM-5 as, "a traumatic event that threatens injury, death, or the physical integrity of self or others and also causes horror, terror, or helplessness at the time it occurs and overwhelms a person's ability to cope" (Agorastos et al., 2019). Whether the victim directly experiences or witnesses the traumatic experience, childhood trauma can include anything from bullying, war exposure, terrorism, food insecurity, housing instability community violence, or childhood abuse and neglect (De Bellis & Zick, 2014; Hunter & Flores, 2020). According to the Center for Disease Control, childhood maltreatment can be split into two main categories: acts of commission and acts of omission (Leeb et al., 2008).

While acts of commission are defined by deliberate and overt behaviors to bring the child harm, acts of omission are forms of neglect that reflect the failure of the caregiver to protect the child from harm exposure or to provide for their basic fundamental needs (Leeb et al., 2008). In most studies of childhood abuse, *Teicher et al.* explains that the most common classifications of maltreatment are physical, sexual, and emotional abuse as well as physical and emotional

neglect. As the use of physical force to cause or potentially result in physical injury against a child, physical abuse can include acts such as hitting, punching, shoving, dropping, shaking, burning, or strangling (Leeb et al., 2008). Sexual abuse, on the other hand, refers to and includes any completed or attempted forms of sexual contact, behavior, or exploitation of a child by an adult (Leeb et al., 2008). Emotional abuse, sometimes referred to as psychological abuse, excludes physical contact and instead involves the usage of verbal and behavioral violence with the intent of terrorizing or isolating the child to believe that they are unwanted, endangered, and unsafe; these behaviors can include humiliation, intimidation, restraint, and confinement (Leeb et al., 2008). As the most common form of childhood maltreatment, neglect can include the failure to meet the child's physical needs in nutrition, hygiene, and shelter or the denial of emotional responsiveness, nurturance, and affection to the child (Cohen et al., 2017).

When there is chronic exposure to such stressors during developmentally vulnerable periods of neurobiological and psychological development like childhood, these prolonged disruptions can lead to worse outcomes in adulthood, such as poor cognitive and social functioning, impaired physiological homeostasis, abnormal activation of stress systems, as well as increased risk for future morbidities (Bremner, 2003; Hughes et al., 2017; Agorastos et al., 2019). For example, human studies have found that early life stressors such as childhood abuse can lead to neurobiological changes in adulthood such as abnormalities in the activity of hypothalamic-pituitary-adrenal (HPA) and norepinephrine systems as well as decreased cortical thickness and diminished myelination between visual and limbic brain areas (Bremner, 2003; Teicher et al., 2016; Agorastos et al., 2019).

Childhood Trauma and Psychiatric Illness

Adverse childhood experiences appear to increase the likelihood of developing a variety of health conditions, including such as coronary heart disease, diabetes mellitus, and psychiatric disorders (Kessler et. al., 1997; Read et. al., 2005; Kubzansky et al., 2009; De Bellis and Zisk, 2014; Hughes et al., 2017). Multiple risk factors early in life have been implicated in schizophrenia risk, including obstetric complications and urbanicity. Similarly, adverse experiences have been a key research area in the exploration of how environmental factors may be implicated in complex psychiatric disorders like schizophrenia (Stilo & Murray, 2019). Trauma exposure is common in the general population, with several studies, including a cross-continental survey of 125,718 adults, finding that anywhere between 47% and 70% of their general population participants have experienced at least one traumatic event (Benjet et al., 2016; Do et al., 2019).

Though trauma exposure appears to be common in general populations, research has shown that those with severe mental illnesses are more likely to have been experienced a traumatic event and are also more likely to have post-traumatic stress disorder as a comorbidity than their non-psychiatric counterparts (Kessler et al., 1995; Mueser et al., 1998). For example, one study found that 91% of a community mental health consumer sample had reported at least one traumatic event exposure, with 55% of that total sample experiencing sexual abuse, 58% experiencing physical assault, and 37% witnessing violence (Cusack et al., 2004). In that same vein, several studies have found that most of their psychiatric patient samples reported at least one traumatic experience, with prevalence ranging from 61% to 82% (Bernstein et al., 1994; McFarlane et al., 2001; Larsson et al., 2013; Negele et al., 2015).

When comparing individuals with psychotic disorders vs non-psychotic psychiatric

disorders, trauma exposure is particularly prevalent in populations with psychotic diagnoses. For example, Spence et al. found that in their sample of psychiatric patients, 75% of their psychosis group had at least one childhood trauma exposure while only 23% of their non-psychosis group had a trauma exposure. For schizophrenia populations, several studies compiled in a systemic review and meta-analysis indicated that the presence of childhood abuse is associated with more severe psychopathology, including heightened anxiety-related symptoms, hallucination severity, and negative symptoms (Bailey et al., 2018). Specifically, they found that total childhood trauma, childhood neglect, and childhood sexual abuse each had significant associations with severity of hallucinations, whereas negative symptom severity was significantly positively correlated with childhood neglect.

Childhood Trauma and Inflammation in Schizophrenia

Childhood trauma is not only prevalent in and associated with more severe psychopathology in psychiatric patient populations but is also linked with increased systemic inflammation in adulthood (Leverich et al., 2002; Fan et al., 2007; Alvarez et al., 2011; Schwandt et al., 2012). In general populations, Hartwell et al. (2013) and Carpenter et al. (2010), both found that there was a positive correlation between adverse childhood experiences and pro-inflammatory IL-6 and CRP levels. Several other studies have found that elevated CRP levels in adulthood are associated with childhood trauma exposure as well as post-traumatic stress disorder diagnoses (Schrepf, et. al., 2014; Lin et. al., 2016; Powers et al., 2019). One meta-analysis that assessed inflammatory phenotypes in adults with or without early life adversity found through random effects meta-analysis of 25 articles that those who had childhood trauma also had elevated baseline levels of CRP, IL-6, and TNF-α as adults. In addition to assessing

childhood trauma overall against these inflammatory markers, Baumeister et al. (2015) analyzed articles that explored if certain subtypes of trauma (sexual abuse, physical abuse, emotional abuse) had differential effects on the inflammatory blood levels. Through meta-regression analyses, Baumeister et al. found that physical and sexual abuse were significantly associated with IL-6 and TNF-α, but not CRP. Though the studies they included on emotional abuse did not measure TNF-α, their data suggests that emotional abuse does not have a statistically significant relationship with either CRP or IL-6. While none of the three major subtypes of abuse were found to have a significant relationship with CRP, Baumeister et al. did show a correlation between parental absence – a form of childhood neglect – and CRP.

In addition, multiple pre-clinical and human studies have demonstrated a strong association between early life stress, which may include trauma, and increased inflammatory markers. For example, Alley et al. (2006) found that those who lived significantly below the United States poverty line had significantly higher CRP levels relative to their counterparts who were above the poverty line. Alley et al. (2006) summarizes that lower socioeconomic status (SES) could be resulting in abnormal inflammatory responses via these individuals living in environments where they are more susceptible to infection as well as have less access to healthcare and related treatments for ailments. Additionally, the present study summarizes that those of lower SES backgrounds are at risk of experiencing higher levels of psychological stress due to also being vulnerable to engaging in risky behaviors. Given the associations between external stress and inflammation, it makes sense that SES could be involved in CRP concentrations.

As an environmental exposure, childhood trauma has been implicated in the psychopathology and physiological dysfunction of schizophrenia. In addition to various studies

linking childhood trauma to elevated hair cortisol concentrations and blood cortisol levels in individuals with schizophrenia (Ryan et al., 2004; Aas et al., 2019), early adverse experiences have been associated with increased IL-6 and TNF-α levels (Dennison et al., 2012) as well as worsened cognitive performance in schizophrenia patients (Shannon et al., 2011). More specific findings emerge when examining different types of childhood trauma. Larsson et al. found that emotional neglect, followed by physical abuse and physical neglect, was the most common form of childhood trauma in their sample of schizophrenia patients. Interestingly, Kilian et al. found that childhood neglect, but not abuse, was positively correlated with poorer premorbid academic adjustment in first-episode schizophrenia spectrum disorder patients. Additionally, one study of 148 schizophrenia patients and 123 bipolar disorder patients found that not only those with childhood abuse (physical, sexual, or emotional) had elevated high-sensitive CRP (hsCRP) levels relative to those without trauma, but also those with all three subtypes of childhood abuse had the highest hsCRP levels (Aas et al., 2017).

Childhood Trauma and Negative Symptoms in Schizophrenia

In addition to increased concentrations of pro-inflammatory markers in a subgroup of patients with schizophrenia, specific childhood trauma subtypes have been correlated with worse negative symptoms (Vogel et al., 2009; Rajkumar, 2015; Bailey et al., 2018). For example, Bailey et al. found that childhood physical and emotional neglect were significantly associated with negative symptom severity when they performed a meta-analysis of 8 different studies. Rajkumar et al. also showed a relationship between PANSS negative symptoms and the CTQ Physical Neglect subscore, but only after stratifying analyses to patients with the most severe

negative symptom scores. Vogel et al. suggested that like dissociation in post-traumatic stress disorders, negative symptoms may be the manifestation of another cognitive and emotional defense against psychological distress for schizophrenia populations that have also experienced adverse childhood experiences. This proposal coincides with their 2009 finding that showed an association between physical neglect and posttraumatic dissociation in schizophrenia populations (Vogel et al., 2009).

Purpose and Hypotheses of the Present Study

As a multifactorial disorder, environmental factors play an important role in the development of schizophrenia, especially if the genetic predispositions are present (Tsuang et al., 2001; Howes et al., 2004). While research has indicated relationships between trauma and inflammation, trauma and schizophrenia, inflammation and negative symptoms, as well as childhood neglect and negative symptoms, there is limited research on the relationships between childhood trauma exposure, increased concentrations of pro-inflammatory markers and negative symptoms in schizophrenia patients.

Considering past literature has identified a positive association between both inflammation and negative symptoms of schizophrenia as well as childhood trauma and psychopathology severity in schizophrenia populations, this study is designed to explore the relationship between childhood trauma, inflammation, and negative symptoms in adult patients with schizophrenia. We hypothesized that pro-inflammatory cytokines would be positively correlated with negative symptoms as well as childhood trauma prevalence (Carpenter et al., 2010; Hartwell et al., 2013; Lee et al., 2014; Goldsmith et al., 2018). Additionally, we

hypothesized that childhood physical and emotional neglect, rather than the other childhood trauma subtypes, will be positively associated with greater negative symptoms (Rajkumar, 2015).

Methods

Subjects

50 patients diagnosed with either schizophrenia or schizoaffective disorder were recruited from psychiatric outpatient clinics at Grady Memorial Hospital (GMH) in Atlanta, Georgia. All of the included subjects were between the ages of 18 and 59, fluent English speakers and had given informed written consent. Patients were carefully screened for medical comorbidities and medication use that could impact markers of inflammation. Regarding medical comorbidities, we excluded those who had concurrent diagnoses of HIV, hepatitis B, or hepatitis C, or if they had a history of central nervous system trauma, active seizure disorder, or evidence of thyroid, cardiovascular, hematological, renal, neurological disease. Further exclusion criteria included individuals who had psychotropic medication changes less than one month before enrollment, treatment with antiviral or immunomodulatory drugs within six months of enrollment, active treatment with antibiotics, active substance abuse within six months of enrollment, positive urine toxicology screens for psychotropic substances, positive pregnancy tests, and HbA1C $\geq$ 8.5% were excluded because they may impact markers of inflammation.

In addition to completing behavioral questionnaires (see below), each patient was interviewed for psychiatric/medical history and demographic information (i.e. race, biological sex, years of education, smoking history), and provided blood for screening labs and assay of inflammatory markers.

Behavioral and Psychiatric Screenings

The Brief Negative Symptom Scale (BNSS) measures the presence of negative symptoms using a 13-item semi-structured interview that assesses the six main aspects of negative

symptoms: blunted affect, distress, alogia, asociality, anhedonia, and avolition. In addition to measuring the individual domains of negative symptoms, the BNSS can also separate negative symptoms into two factors: Deficits in motivated behaviors (AAA: avolition, asociality, anhedonia) and deficits in expressivity (EXP: alogia and blunted affect) (Kirkpatrick et al., 2018).

The Positive and Negative Syndrome Scale (PANSS) is a 30-item semi-structured interview used to measure the overt psychopathology of schizophrenia. Specifically, 7 categories measure positive symptoms, 7 measure negative symptoms, and 16 measure general psychopathology symptoms. Each category, as well as the overall PANSS score, has been effective in assessing symptom severity for individuals with schizophrenia (Kay et. al., 1987).

The Calgary Depression Scale for Schizophrenia (CDSS) is a 9-item self-report that examines if there is a comorbidity of depression in individuals with schizophrenia; a score of > 6 indicates the presence of clinically significant depression (Addington, et. al., 1993). As a questionnaire that measures depressive symptoms, we wanted to investigate whether the effects of trauma and inflammation might be due to depressive symptoms, given the literature on inflammation and motivational deficits in patients with depression. This assessment has been effective and reliable in assessing depression independently of schizophrenia while also maintaining minimal overlap with positive symptoms (Addington, et. al., 2014).

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-administered questionnaire that identifies the presence as well as the magnitude of five types of childhood trauma: physical neglect, emotional neglect, physical abuse, emotional abuse, and sexual abuse. 5 questions are allocated for each trauma sub-type, with the 3 remaining questions being a part of a minimization/denial scale that measures the presence of under-reporting or understatement of

childhood trauma (Liebschutz et. al., 2018). Each question, with the exception of some which are reverse coded, are on a 5-point scale (1 = Never True, 2 = Rarely True, 3 = Sometimes True, 4 = Often True, 5 = Very Often True).

Blood Draw and Laboratory Samples

Blood samples were collected from each participant on two occasions. During a screening visit, subjects provide a non-fasting blood sample and the following lab variables were measured: C-reactive protein (CRP), Hemoglobin A1C (HbA1C), as well as various screening labs including a full chemistry panel and complete blood cell count. CRP is assayed using a high sensitivity turbidimetric assay at a GMH CLIA-certified laboratory. CRP can be further categorized as low or high based on American Heart Association/Centers for Disease Control guidelines for cardiovascular disease: low (CRP $\leq$ 3 mg/L) and high (CRP > 3 mg/L) (Ridker, 2003). During Visit 2, blood plasma was collected and a subset of the sample (n = 37) had blood assayed for high-sensitivity CRP (hsCRP), TNF-α, soluble tumor necrosis factor receptor 2 (sTNFR2), interleukin-1 receptor antagonist (IL-1ra), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6), soluble interleukin-6 receptor (sIL-6R), and monocyte chemoattractant protein-1 (MCP-1) plasma levels via Fluorokine MAP Multiplex Human Biomarker Panels.

Statistical Analyses

All analyses were conducted on RStudio Desktop Open Source Edition and SPSS (Version 27). Because 4 patients left one of the 28 items on the CTQ blank, we dealt with missing data by calculating the average of the other items contributing to that subscale score and replacing the missing item with that number. Descriptive statistics (e.g., means, median, and

standard deviations) were computed for the sample's demographic variables, laboratory results, and behavioral questionnaire scores.

The inflammatory marker concentrations were not normally distributed so were natural log transformed for statistical analyses. We first used bivariate non-parametric correlations to test the association between CTQ total and subscale scores with BNSS and PANSS scores (total and subscale) as well as the individual inflammatory markers. Three of the enrolled subjects did not have scores collected for the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS), leaving 47 subjects to be analyzed for these measures. Given our a priori hypotheses regarding associations between inflammatory markers and negative symptoms, we split the sample using a median split of the BNSS motivated behaviors factor (AAA: avolition, asociality, anhedonia). We then ran correlations between individual inflammatory marker concentration and CTQ total and subscale scores. Finally, in exploratory analyses, we created four groups based on the BNSS AAA median split and high/low CRP (using a cutoff of 3mg/L based on Center for Disease Control and American Heart Association guidelines) (Ridker, 2003) and again tested correlations between individual inflammatory marker concentrations and CTQ total and subscale scores.

Results

Sample Demographic, Behavioral, and Blood Characteristics

The mean and standard deviation, as well as distribution, of demographic factors, laboratory results, and behavioral questionnaire scores for the enrolled subjects (n = 50) can be found in Tables 1-3.

As seen in Table 1, the participants had a mean age of 40.78 (SD = 12.45), had a mean BMI of 32.91 (SD = 8.45), and were almost evenly split between smokers and non-smokers. Additionally, the majority identified as black (n = 41) or male (n = 34), with half of the sample completing some amount of a college education (n = 25). The mean and standard deviation values for each inflammatory marker can be found in Table 2. The median screening CRP level of these participants was 2.9. (Table 2).

As seen in Table 3 and Figure 1, the mean total Childhood Trauma Questionnaire (CTQ) of the sample (n = 50) is 48.01 (SD = 15.48). The mean Brief Negative Symptom Scale (BNSS) total score was 31.80 (SD = 11.88), and the deficits in motivated behaviors (AAA: avolition, asociality, anhedonia) and deficits in expressivity (EXP: alogia and blunted affect) subscales had means of 18.34 (SD = 7.73) and 11.74 (SD = 11.70), respectively (Figure 2, Table 3).

Three of the enrolled subjects did not have scores collected for the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS), leaving 47 subjects to be analyzed for these measures.

Bivariate Correlations

Bivariate Spearman correlations between the CTQ Total Score and the Individual Subscales with Symptoms Measures and Inflammatory Markers can be found in Tables 4-6. We

found a positive correlation between CTQ Total and PANSS Positive scores (r=0.462, p<0.001), as well as positive correlations between all CTQ subscales and PANSS Positive symptom scores. Regarding the individual CTQ subscale items, we found that CTQ Physical Neglect was positively correlated with BNSS AAA (r=0.299, p=0.035), as well as the BNSS Anhedonia (r=0.303, p=0.032). CTQ Physical Neglect also had a positive trend with BNSS Avolition (r=0.3249, p=0.082). CTQ Emotional Neglect was positively correlated with BNSS AAA (r=0.307, p=0.030), BNSS Anhedonia (r=0.294, p=0.038), and BNSS Asociality (r=0.294, p=0.038). Given our hypotheses regarding the impact of inflammation on negative symptoms and the observed relationships between the CTQ Neglect Subscores and the BNSS AAA Factor Score (and individual items), we next stratified the sample into a low and high BNSS AAA Factor groups based on a median split (median BNSS AAA = 17.0).

Spearman correlations were then conducted between each inflammatory marker and the CTQ subscales for each subgroup. The complete correlation results can be found in Tables 7-8. We did not find any significant correlations for the low BNSS AAA score subgroup. We did not find any significant correlations for the high BNSS AAA score subgroup. However, we did find several positive trends between inflammatory markers and CTQ. In the high BNSS AAA subgroup, we found that CTQ Emotional Abuse had showed trends for positive correlations with sIL-6R (r=0.397, p=0.083) and TNF-α (r=0.444, p=0.050). Similarly, CTQ Physical Abuse showed trends toward significant positive correlations with sIL-6R (r=0.385, p=0.093) and TNF-α (r=0.396, p=0.084). In addition to those with two CTQ Abuse subscales, there was a trend toward a positive correlation between CTQ Physical Neglect and TNF-α (r=0.387, p=0.092).

To explore the relationships between inflammatory markers, negative symptoms, and childhood trauma exposure, we further split the sample into four groups based on different

combinations of Low/High BNSS AAA Factor scores and Low/High CRP levels (the cut off was 3mg/L, as per CDC/AHA guidelines; Ridker, 2003). The full results for these exploratory analyses are located in Tables 9-12. We did not find any statistically significant positive correlations for either the Low BNSS AAA/Low CRP subgroup or the Low BNSS AAA/High CRP subgroup. However, we did find a positive trend between CTQ Physical Abuse and sIL-6R (r=0.587, p=0.096) in the Low BNSS AAA/High CRP subgroup. In the High BNSS AAA/Low CRP group, we found that CTQ Emotional Abuse had a positive correlation with sIL-6R (r=0.596, p=0.041). We also found a positive trend for the correlations between CTQ Sexual Abuse and TNFR2 (r=0.498, p=0.099) as well as that between CTQ Emotional Neglect and sIL-6R (r=0.523, p=0.081). In the High BNSS AAA/High CRP group, there was a significant positive correlation between CTQ Physical Neglect and IL-6 (r=0.776, p=0.024) (Figure 7).

Discussion

Accounting for more than $60 billion annually in the United States, schizophrenia is a complex and debilitating psychiatric illness that is characterized by a combination of positive and negative symptoms (Chong et al., 2016). Schizophrenia has been linked with various clinical comorbidities, such as excess early mortality as well as increased risk for suicide, tobacco smoking, obesity, cardiovascular disease (Ryan & Thakore, 2004), as well as socioeconomic adversities such as homelessness and unemployment (Foster et al., 2012; Evensen et al., 2016). Given the immense burdens posed on both those diagnosed with schizophrenia as well as those around them, there has been a greater focus on examining the biological mechanisms and environmental factors behind schizophrenia. There is increasing evidence that inflammation and childhood trauma may be implicated in the psychopathology of schizophrenia (Dennison et al., 2012; Bulzacka et al., 2016; Goldsmith et al., 2018; Bailey et al., 2018).

We found that both CTQ Neglect Subtypes were positively correlated with the BNSS AAA factor which represents the deficits of motivated behavior domain of negative symptoms. In individuals with high BNSS AAA scores, we identified positive trends for a relationship between TNF-α with CTQ Total, as well as with the Emotional Abuse and Physical Neglect subscales. Additionally, in exploratory analyses, we found a positive correlation between the pro-inflammatory cytokine IL-6 with the CTQ Physical Neglect subscale in a subgroup of patients with both high BNSS AAA scores and high CRP.

Relationship between Inflammation, Childhood Trauma, and Negative Symptoms

The CTQ Total Score and the Individual Subscales were positively associated with PANSS Positive Symptoms scores, suggesting that childhood trauma of any type was associated

with worse positive symptoms, including delusions and hallucinations. We also found that both CTQ Neglect Subscales were correlated with the BNSS AAA and BNSS Anhedonia subscales and CTQ Emotional Neglect also was positively correlated with BNSS Asociality. We did not find any relationship between the CTQ measures and PANSS negative symptom subscale, though the PANSS negative symptoms subscale may not accurately reflect the full range of negative symptoms (Daniel, 2013; Saleh et al., 2021) that the BNSS captures.

When the sample was split into two groups based on their BNSS AAA score, we found a number of intriguing trends for associations between inflammatory markers and CTQ scores, including associations between sIL-6R and TNF. Finally in exploratory analyses, we found a positive association between IL-6 and the CTQ Physical Neglect subscale in a subgroup of patients with high inflammation (as indexed by CRP) and high BNSS AAA score.

The association between the PANSS Positive Symptom Subscale with all of the CTQ Total Score and the Individual Subscales aligns with a large literature that identifies childhood trauma as being an environmental risk factor for the development of psychosis and related psychotic disorders (Read et al., 1999; Janssen et al., 2004; Bendall et al., 2008; Beards et al., 2013) as well as findings correlating childhood maltreatment with psychosis severity, including hallucinations (Alvarez et al., 2011; Bailey et al., 2018). Several recent studies have focused on establishing models that propose potential pathways from childhood trauma to psychosis in adulthood. For example, one review summarizes that childhood trauma may be implicated in psychosis via various biological mechanisms, including the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis or the overactivation of the immune system and its inflammatory response (Misiak et al., 2017). Some studies suggest that traumatic events in childhood may be implicated in psychosis via triggering the dysregulation of glucocorticoid production.

Considering glucocorticoid receptors are distributed in various dopaminergic pathways, including structures like the striatum and nucleus accumbens, these studies suggest that this abnormal HPA axis activity may be implicated in the overstimulation of striatal dopaminergic pathways (Walker and Diforio, 1997; Read et al., 2001; Craenenbroeck et a l., 2005). This hypothesis is intriguing, considering the widely studied dopamine hypothesis for psychosis suggests that excessive dopamine D2-receptor activation may be triggering psychotic symptoms (Tost et al., 2010) and the vast literature identifying dysregulation of subcortical dopaminergic activity in patients with schizophrenia (Kegeles et al., 2010; Brisch et al., 2014).

In addition to interacting with dopaminergic systems, glucocorticoids act as immune response regulators in a variety of ways. For example, glucocorticoids act as inhibitors of inflammation by reducing the signaling of structures involved in the inflammatory response such as pattern recognition receptors and cytokine receptors (Cain and Cidlowsky, 2017). Though the specific mechanisms are still to be explored, some studies suggest that prolonged elevation of glucocorticoids, such as via extended childhood trauma exposure, can be provoking epigenetic modifications that may be leading to disruptions in glucocorticoid-receptor-mediated pathways (Perroud et al., 2011; Baumeister et al., 2016; Danese and Lewis, 2017). For example, several studies indicate that trauma exposure in key periods of biological development, such as childhood, can be leading to gene expression changes such as increased methylation of glucocorticoid receptor (GR) and increased demethylation of FKBP5 (McGowan et al., 2009; Perroud et al., 2011; Klengel et al., 2012). These modifications are thought to impair GR functioning, and consequentially disrupt their anti-inflammatory activity, thus leading to an elevated inflammatory state later on that is also GR resistant (Baumeister et al., 2016).

The associations between CTQ Physical and Emotional neglect with specific BNSS

negative symptom subscales are consistent with some previous research that has found positive correlations between CTQ neglect subscales and various negative symptoms (Vogel et al., 2011; Gallagher et al., 2013; Rajkumar, 2015; Uyan et al., 2022). One meta-analysis of 8 studies found there to be a significant association between childhood neglect and negative symptom severity (Bailey et al., 2018). Considering the growing literature linking inflammation and negative symptoms, we propose a model in which childhood trauma may be involved in negative symptoms via inflammation. Building off of the literature from the previous paragraph, significant childhood trauma exposure may be causing dysregulations in the immune system, such as its inflammatory response. Given that several studies have identified elevated inflammatory marker concentrations and chronic macrophage activity in schizophrenia patients (Naudin et al., 1997; Erbagci et al., 2001; O'Brien et al., 2008; Beumer et al., 2012; Xiu et al., 2014), it is possible that inflammation may be the stepping stone between childhood trauma as an environmental factor in schizophrenia.

Our findings regarding childhood trauma and negative symptoms align with theoretical pathways that suggest how childhood trauma can lead to negative symptoms later in life. One possible explanation is the traumagenic neurodevelopmental model, which posits that traumatic environmental exposures during childhood can lead to structural and biological changes in neurological development that include aberrant monoaminergic signaling, hypothalamic-pituitary-adrenal (HPA) axis hypersensitivity, as well as structural abnormalities (Read et al., 2001). Another model suggests that the pathway from childhood trauma and psychosis is mediated by the attachment style of the caregiver, such that poor attachment style facilitates the development of negative symptoms from childhood neglect (van Dam et al., 2014).

The fact that the data indicates that childhood neglect was specifically correlated with the

deficits in motivated behaviors (anhedonia, asociality, and avolition) domain of negative symptoms is intriguing because there is growing literature to suggest that inflammation, and specifically TNF, may be associated with negative symptoms in patients with schizophrenia. For example, TNF has been shown to be associated with patients with deficit schizophrenia, characterized by prominent and chronic negative symptom severity (Goldsmith et al., 2018). TNF has also been shown to be associated with the development of negative symptoms in individuals at clinical high risk for psychosis (Goldsmith et al., 2019). One possible mechanism for inflammation's association with negative symptom severity is via its effects on brain reward circuitry (Goldsmith & Rapaport, 2020). Indeed, in recent unpublished data from our group, we have shown that inflammation (as indexed by CRP) was associated with the BNSS AAA factor but not the expressivity factor (Goldsmith et al, unpublished data). Moreover, preliminary data from our group shows that TNF is associated with altered signaling in the ventral striatum in response to reward anticipation and the anterior insula in response to increasing perceived effort (Goldsmith et al., unpublished data), similar to what has been shown in patients with depression. Motivational deficits pose significant challenges to functional recovery and are difficult to effectively treat with the currently available antipsychotic medications (Correll and Schooler, 2020). Negative symptoms have limited treatment options and so exploring the etiology of schizophrenia will inform more effective interventions.

The finding that TNF-α had trend-level positive correlations with CTQ total, CTQ emotional abuse, and CTQ physical neglect is in line with previous work that has found TNF-α to be positively correlated with childhood maltreatment overall (Dennison et al., 2012). Considering TNF-α is a pro-inflammatory cytokine that has been shown to be elevated in first-episode psychosis and chronic schizophrenia patients (Goldsmith et al., 2016), it is intriguing

that this cytokine has a positive association with childhood trauma which is an environmental factor found more prevalently in schizophrenia populations than their non-psychotic counterparts (Spence et al., 2006). Considering several studies have connected TNF-α with not only childhood trauma, but also negative symptoms and altered activity in motivational pathways, the present study's findings suggest that inflammation, and specifically TNF, could be a potential mechanism involving the association of childhood trauma and persistent negative symptoms.

Another interesting finding was the positive correlation between IL-6 and CTQ Physical Neglect in the elevated inflammation and increased motivational deficits subgroup (high CRP/high BNSS AAA). Besides IL-6 being previously linked with a history of childhood trauma and negative symptoms (Carpenter et al. 2010; Dennison et al., 2012; Hartwell et al., 2013; Goldsmith et al., 2018; Pedrotti Moreira et al., 2018), IL-6 is thought to both work in tandem with and be induced by TNF-α. In addition to both being implicated in the activation of immune responses, TNF-α prompts the release of IL-6 through activating the inhibitory kappa B factor (NFκB) pathway that ultimately activates the transcription of pro-inflammatory cytokines through binding with NFκB responsive genes (Tanabe et al., 2010). Though TNF and IL-6 are not significantly correlated in this sample, it is intriguing that two of the commonly increased proinflammatory cytokines in patients with schizophrenia (Goldsmith et al., 2016) that have also been shown to be associated with negative symptom severity (Goldsmith et al., 2018) are associated with physical neglect. Future work should seek to test the causal role of inflammation in these relationships. Finding subgroups of patients for whom inflammation may be driving negative symptoms severity, perhaps through a history of childhood trauma, could lead to novel interventions that would support precision medicine.

Limitations

While the results support relationships between inflammation with childhood neglect in subtypes of schizophrenia with worse negative symptoms, there are several limitations in the current study that are worth noting. Our sample had a total CTQ score that would be considered low to moderate childhood trauma exposure (Bernstein & Fink, 1998). Less than half (n = 16) of the participants fell into the moderate to extreme division of overall childhood trauma exposure severity. When examining the mean totals for each CTQ subscale (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect), most of the trauma subtypes were classified as low to moderate exposure, with the except of sexual abuse which was moderate to severe for this sample (Bernstein & Fink, 1998). Though trauma exposure is more prevalent in populations with psychotic disorders relative to those with non-psychotic disorders (Spence et al., 2006), this suggests that we may expect to see greater associations between inflammation and negative symptoms in a more trauma-exposed sample.

In addition to low trauma exposure, another limitation of the study is the small sample size. With only 50 patients enrolled in the present study, our small sample size may have impaired our ability to uncover stronger associations between inflammation markers, childhood trauma, and negative symptoms. This limitation particularly came into play when running correlation analyses on the various negative symptom and inflammation subgroups. When looking at the four combinations of Low/High BNSS AAA and Low/High CRP, our correlations ranged in subgroup sample size from 8 to 15. Furthermore, with a larger sample size, we would also have had more statistical power to expand on our correlation findings via subsequent mediation analyses.

The present study employed a cross-sectional design, such that data from each subject

was collected in one given time. With that being said, the absence of the temporal link prevents us from exploring these relationships between childhood trauma, inflammation, and negative symptoms in schizophrenia with more directionality and from developing causal inferences. As a means of advancing our understanding of the interactions between these variables, a longitudinal study design would be a more ideal choice.

Future Directions

Though the small size and relatively low trauma exposure of our sample may impede our ability to generalize our findings to a larger population, the present study builds on previous work based on the interactions between socioenvironmental factors and biology in the development of complex disorders. More specifically, we explored how childhood trauma may be associated with inflammation and negative symptom severity in adult patients with schizophrenia.

The current study is one of the few to investigate associations between childhood trauma, inflammation, and negative symptoms in individuals with schizophrenia. Furthermore, while most of the studies investigating cytokines and their role in psychiatric disorders only include one or two specific inflammatory markers, this study expands upon previous research by including a larger panel of seven different inflammatory markers. Investigating a larger panel of inflammatory markers enables a more nuanced investigation of how inflammation may be implicated in childhood trauma and symptoms of schizophrenia.

Considering this research is a part of an ongoing study that continues to enroll patients, it would be worthwhile to reassess these relationships once a greater sample size has been achieved. With a greater sample size, more statistically powerful correlation analyses can be

performed as well as more directional analyses such as that of linear regression and mediation modeling.

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Tables and Figures

Table 1

Demographic Characteristics

Characteristics	*No.*	*Mean (SD) or %*
Demographics		
Sex	**50**	
Male	34	68.0%
Female	16	32.0%
Age (years)	**50**	**40.78 (12.45)**
BMI	**50**	**32.91 (8.45)**
Race		
White	6	12.0%
Black	41	82.0%
Multi-Racial or Other	3	6.0%
Education Level	**50**	
8th Grade or Less	1	2.0%
Some High School	12	24.0%
High School Graduate/GED	12	24.0%
Some College	13	26.0%
College Graduate (At Least Associate)	8	16.0%
Business and Technical College Beyond High School	4	8.0%
Nicotine Smoking Status	**50**	
Smoker	26	52.0%
Non-Smoker	24	48.0%

Table 2

Laboratory Blood Serum Characteristics

Measures	*No.*	*Mean (SD) or %*	*Median*
Screening CRP (mg/L)	**50**		2.9
Visit 2 CRP (mg/L)	**37**		1.91
MCP-1 (pg/mL)	**37**	154.55 (38.10)	144.04
sIL-6R (pg/mL)	**37**	33234.84 (6412.94)	32704
IL-1RA (pg/mL)	**37**	489.52 (287.02)	395.07
sTNFR2 (pg/mL)	**37**	1897.36 (499.98)	1740
TNF-α (pg/mL)	**37**	3.62 (1.17)	3.58
IL-1β (pg/mL)	**37**	0.25 (0.17)	0.17
IL-6 (pg/mL)	**37**	0.85 (0.48)	0.77

Table 3

Behavioral Questionnaire Scores: CTQ, BNSS, PANSS, and CDSS

Measures	*No.*	*Mean (SD) or %*	*Median*
CTQ Scores	**50**		
Total	50	48.01 (15.48)	
Physical Abuse	50	8.72 (3.42)	
Emotional Abuse	50	8.97 (4.32)	
Sexual Abuse	50	9.12 (5.06)	
Physical Neglect	50	9.09 (3.54)	
Emotional Neglect	50	11.56 (5.94)	
BNSS Scores	**50**		
Total	50	31.80 (11.88)	
AAA Subscore	50	18.34 (7.73)	17.00
Anhedonia	50	12.46 (11.35)	
Asociality	50	4.46 (2.37)	
Avolition	50	4.97 (2.63)	
EXP Subscore	50	11.74 (7.11)	12.00
Blunted Affect	50	6.69 (4.79)	
Alogia	50	5.31 (4.26)	
Distress	50	2.37 (2.40)	
PANSS Scores	47		
Total	47	65.16 (15.42)	
Negative Subscale	49	17.92 (5.82)	
Positive Subscale	49	15.57 (5.77)	
General Psychopathy Subscale	47	31.36 (8.62)	
CDSS Score	47		
Total	47	4.81 (4.25)	

Table 4

Spearman Correlations of Childhood Trauma (CTQ) with Brief Negative Symptom Scale (BNSS)

	BNSS Total	BNSS Anhedonia	BNSS Asociality	BNSS Avolition	BNSS Distress	BNSS Blunted Affect	BNSS Alogia	BNSS AAA	BNSS EXP
Childhood Trauma Total	.039	.200	.043	.104	-.062	-.167	-.074	.165	-.145
Childhood Emotional Abuse	.035	.227	.152	.030	-.140	-.152	-.075	.180	-.142
Childhood Physical Abuse	.006	.099	-.111	.041	-.073	-.119	-.076	.055	-.123
Childhood Sexual Abuse	-.055	-.072	-.217	-.060	.146	-.050	-.003	-.117	-.029
Childhood Emotional Neglect	.050	.294*	.294*	.182	-.205	-.264^	-.131	.307*	-.222
Childhood Physical Neglect	.169	.303*	.150	.249^	.020	-.054	-.013	.299*	-.022

Note. $N = 50$

$^{\wedge}p < .10.$ $^{*}p < .05.$ $^{**}p < .01.$

Table 5

Spearman Correlations of Childhood Trauma (CTQ) with Positive and Negative Symptoms Scale (PANSS)

	PANSS Total[1]	PANSS Positive[2]	PANSS Negative[2]	PANSS General Psychopathology[1]
Childhood Trauma Total	.225	.462**	-.122	.202
Childhood Emotional Abuse	.346*	.492**	.001	.298*
Childhood Physical Abuse	.095	.305*	-.173	.093
Childhood Sexual Abuse	.099	.376**	-.274^	.137
Childhood Emotional Neglect	.275^	.400**	.019	.247^
Childhood Physical Neglect	.226	.327*	.107	.110

Note.

1. $N = 47$
2. $N = 49$

$^{\wedge}p < .10.$ $^{*}p < .05.$ $^{**}p < .01.$

Table 6

Spearman Correlations of Childhood Trauma (CTQ) with Calgary Depression Scale for Schizophrenia (CDSS)

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
CDSS Total	.222	.324*	.004	.105	.261^	.148

Note. $N = 47$

$^{\wedge}p < .10.$ $^{*}p < .05.$ $^{**}p < .01.$

Table 7

Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: Low BNSS AAA Score Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =20)	.199	.296	.172	.319	-.110	-.135
SIL-6R (N =20)	.088	-.010	.440^	.014	-.205	-.028
IL-1ra (N =20)	.126	.142	.298	.111	.050	.086
TNFR2 (N =20)	-.505*	-.278	-.430^	-.593*	-.146	-.429^
TNF-α (N =20)	-.364	-.298	-.175	-.052	-.383	-.477^
IL-1β (N =20)	.041	.030	.112	.278	-.301	-.308
IL-6 (N =20)	-.022	-.200	-.113	.068	-.169	.058
CRP (N =27)	-.391	-.505*	.020	-.085	-.449*	-.247

^$p < .10$. *$p < .05$. **$p < .01$.

Table 8

Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: High BNSS AAA Score Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =17)	.090	.105	-.088	-.046	.241	-.107
SIL-6R (N =17)	.261	.397^	.385^	.147	.174	.030
IL-1ra (N =17)	-.015	-.100	-.288	.178	.047	-.026
TNFR2 (N =17)	.002	-.074	.056	.198	-.047	-.218
TNF-α (N =17)	.431	.444^	.396^	.281	.306	.387^
IL-1β (N =17)	-.085	-.173	-.264	-.087	.127	-.147
IL-6 (N =17)	.251	.042	.232	.149	.233	.227
CRP (N =22)	-.157	-.166	-.010	-.085	-.123	-.032

$^{\wedge}p < .10$. $^{*}p < .05$. $^{**}p < .01$.

Table 9

Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: Low BNSS AAA Score and Low CRP Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =11)	.383	.443	.259	.454	-.303	-.590
SIL-6R (N =11)	.381	.333	.168	.049	-.060	.358
IL-1ra (N =11)	.500	.167	.395	.146	.446	.469
TNFR2 (N =11)	-.333	.095	-.838**	-.805*	.602	.198
TNF-α (N =11)	-.762*	-.524	-.551	-.464	-.060	-.494
IL-1β (N =11)	.277	.265	.267	.346	-.341	-.513
IL-6 (N =11)	.190	-.071	-.120	.268	.084	.544
CRP (N =14)	-.571^	-.535	-.552^	-.151	-.248	-.281

^$p < .10$. *$p < .05$. **$p < .01$.

Table 10

Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: Low BNSS AAA Score and High CRP Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =9)	.050	.262	.094	.068	.046	-.035
SIL-6R (N =9)	.083	-.157	.587^	.111	-.165	-.140
IL-1ra (N =9)	-.267	-.061	.162	-.179	-.239	-.376
TNFR2 (N =9)	-.683*	-.586^	-.204	-.485	-.633^	-.743*
TNF-α (N =9)	-.085	-.031	.104	.313	-.534	-.290
IL-1β (N =9)	-.067	.026	-.043	.124	-.304	-.061
IL-6 (N =9)	-.336	-.339	-.146	-.193	-.439	-.481
CRP (N =13)	-.497	-.550^	-.207	-.236	-.383	-.270

^$p < .10$. *$p < .05$. **$p < .01$.

Table 11

Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: High BNSS AAA Score and Low CRP Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =12)	.154	.286	-.163	-.334	.389	.173
SIL-6R (N =12)	.484	.596*	.454	.105	.523^	.131
IL-1ra (N =12)	-.032	-.081	-.355	.221	-.025	.053
TNFR2 (N =12)	.284	.229	.298	.498^	.102	.007
TNF-α (N=12)	.389	.434	.407	.284	.283	.256
IL-1β (N =12)	.136	-.077	.016	.290	.273	-.114
IL-6 (N =12)	.069	-.214	.162	.109	.107	-.174
CRP (N =15)	.116	-.038	.081	.177	-.006	.390

^$p < .10$. *$p < .05$. **$p < .01$.

Table 12

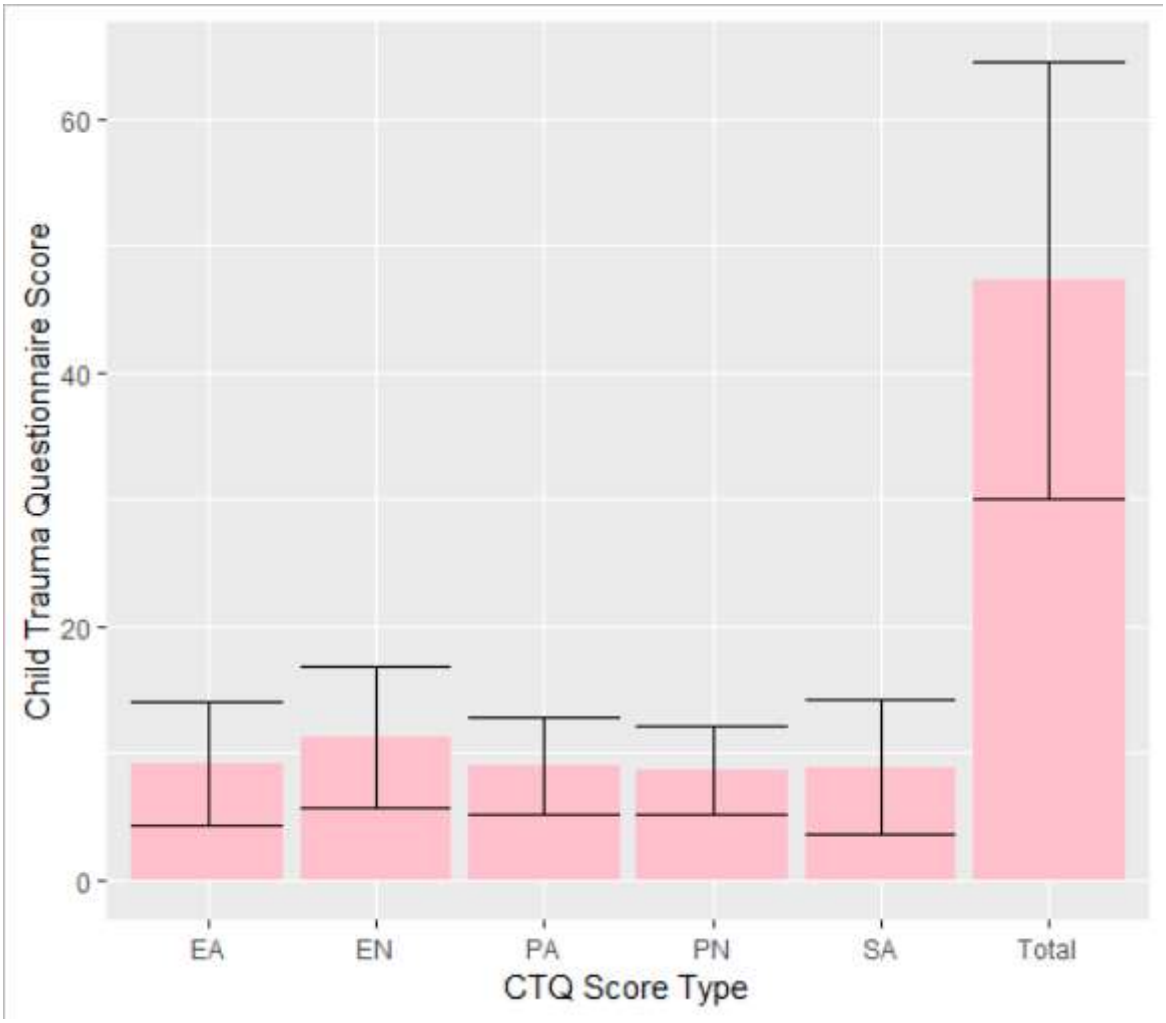
Spearman Correlations of Childhood Trauma (CTQ) with Inflammatory Marker: High BNSS AAA Score and High CRP Group

	Childhood Trauma Total	Childhood Emotional Abuse	Childhood Physical Abuse	Childhood Sexual Abuse	Childhood Emotional Neglect	Childhood Physical Neglect
MCP-1 (N =8)	-.310	-.395	-.293	-.128	-.036	-.554
SIL-6R (N =8)	.024	.024	.073	.217	-.228	-.096
IL-1ra (N =8)	.000	-.084	-.171	.204	.383	-.374
TNFR2 (N =8)	-.262	-.299	-.293	-.038	.036	-.675^
TNF-α (N =8)	.587	.584	.368	.405	.470	.503
IL-1β (N =8)	-.300	-.239	-.641^	-.591	-.038	.076
IL-6 (N =8)	.515	.434	.135	.244	.265	.776*
CRP (N =12)	.056	-.071	.210	.224	-.131	-.166

^$p < .10$. *$p < .05$. **$p < .01$.

Figure 1

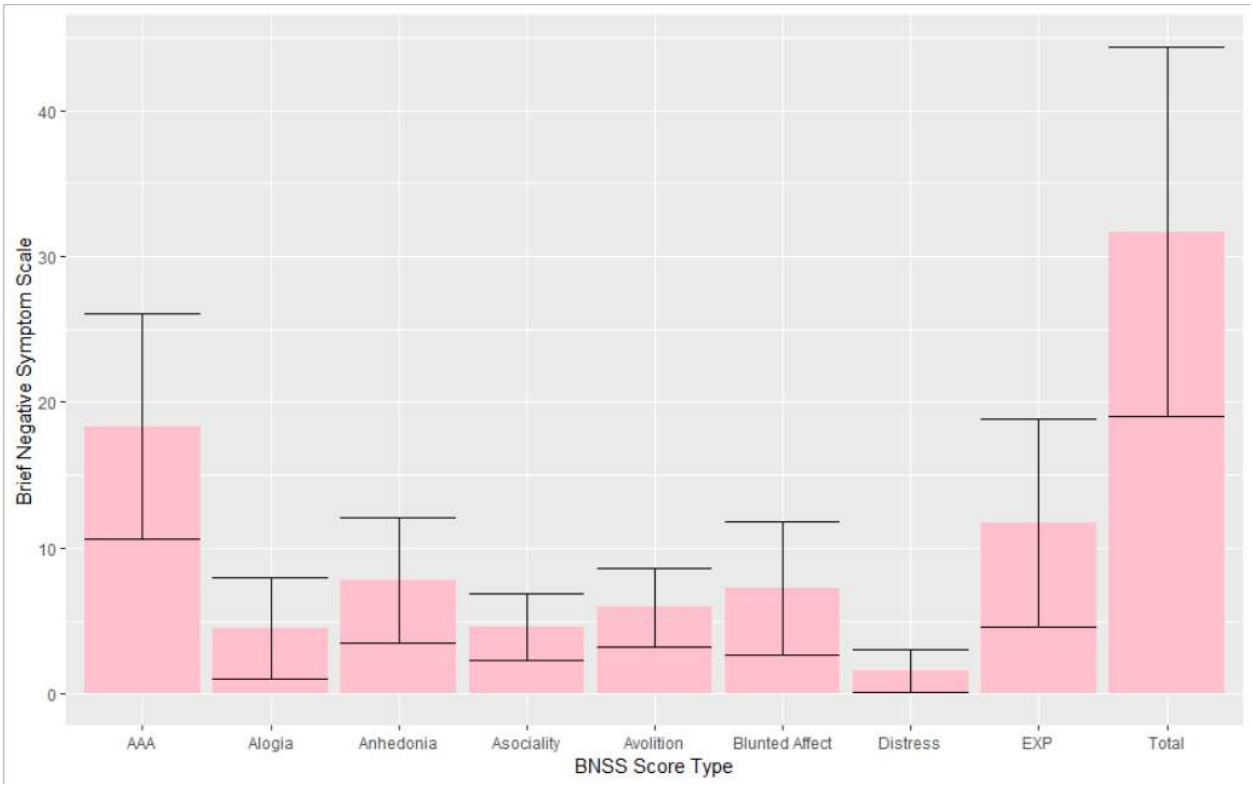
Mean childhood trauma exposure scores of sample population (N = 50) using the Childhood Trauma Questionnaire (CTQ)



Note. *N* = 50. Higher scores indicate more exposure of that specific childhood trauma subtype. Childhood trauma subtypes are coded as follows: Emotional Abuse (EA), Emotional Neglect (EN), Physical Abuse (PA), Physical Neglect (PN), Sexual Abuse (SA), Childhood Trauma Total (Total). Error bars indicate the standard error of the mean.

Figure 2

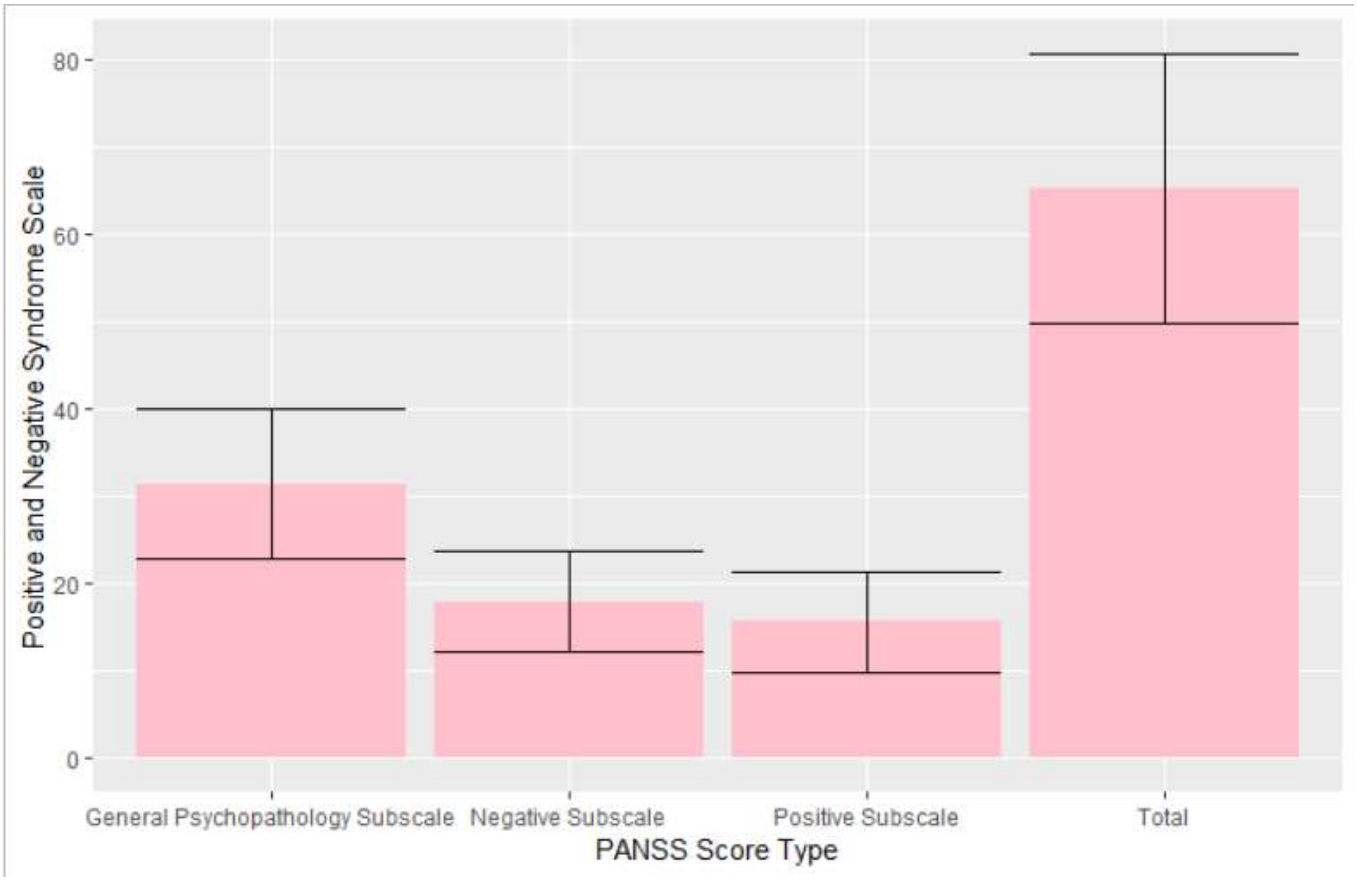
Mean negative symptom scores of sample population using the Brief Negative Symptom Scale (BNSS)



Note. *N* = 50. Higher scores indicate more severe symptoms. In addition to the 6 individual items of the BNSS, this figure includes the two domains of negative symptoms which are coded as follows: Deficits of Motivated Behaviors (AAA) and Deficits of Expressivity (EXP). Error bars indicate the standard error of the mean.

Figure 3

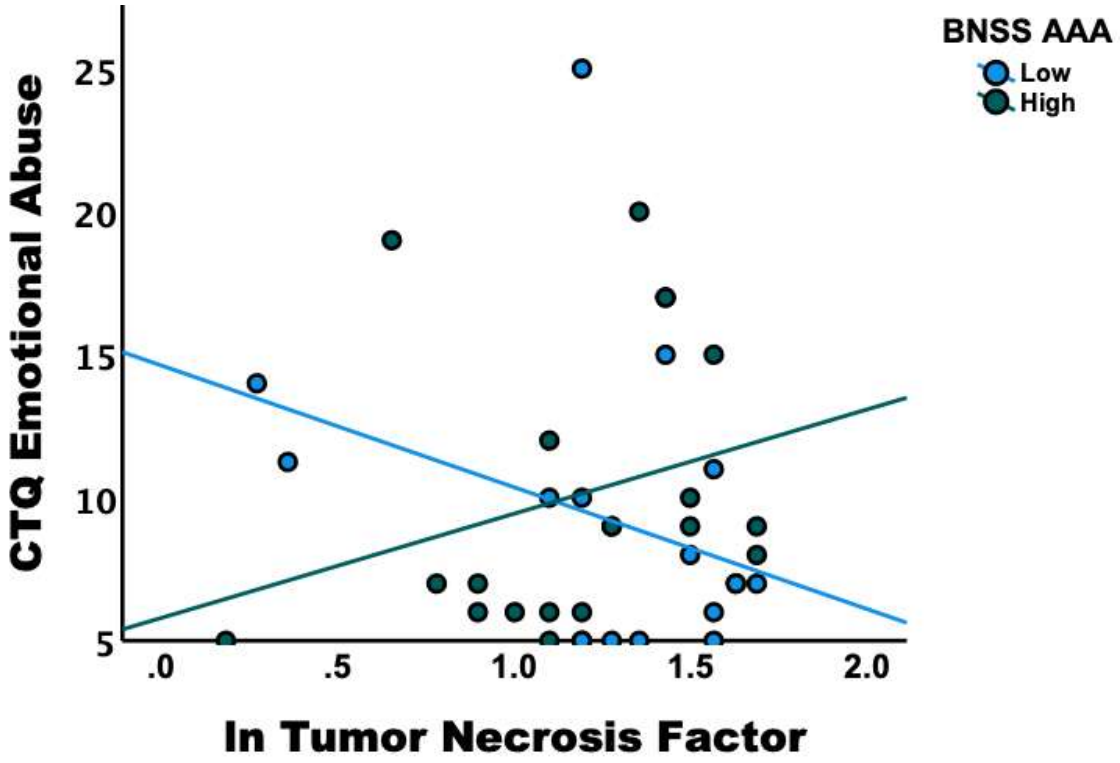
Mean schizophrenia symptom severity scores of sample population using the Positive and Negative Syndrome Scale (PANSS)



Note. *N* = 47 for Total and General Psychopathology Subscale. *N* = 49 for Negative Subscale and Positive Subscale. Higher scores indicate more severe symptoms. Error bars indicate the standard error of the mean.

Figure 4

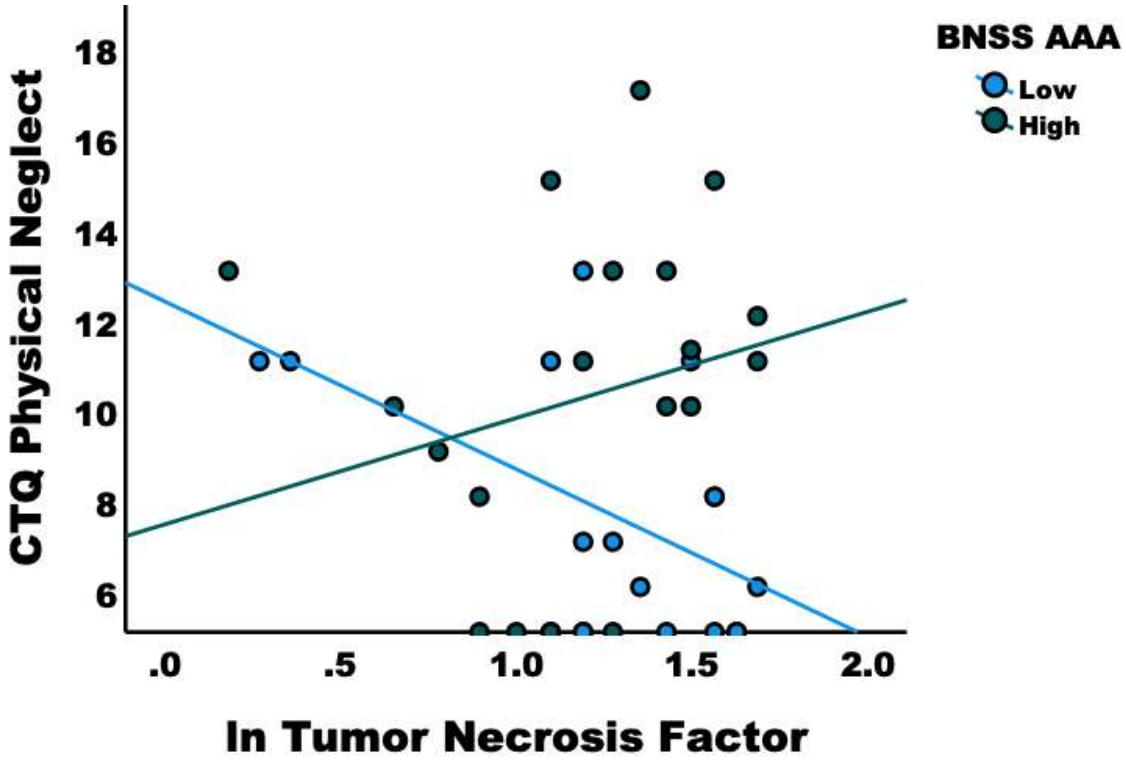
Comparison of the Relationship between Tumor Necrosis Factor and Childhood Trauma Questionnaire Emotional Abuse Subscale Scores for those with Low and High Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. The groups were split based on a median split (17.00) into the two groups. BNSS Low AAA: r=-.298, $p>0.10$. BNSS High AAA: r=.444, $p<0.10$.

Figure 5

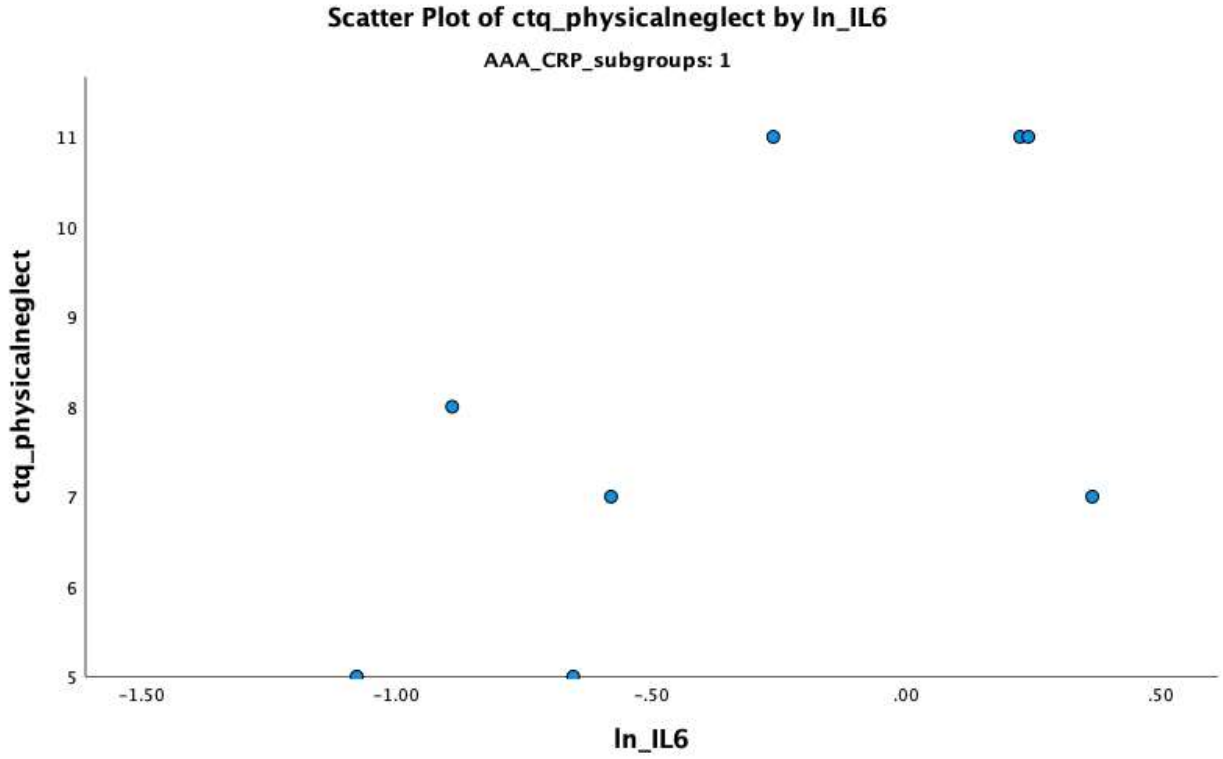
Comparison of the Relationship between Tumor Necrosis Factor and Childhood Trauma Questionnaire Physical Neglect Subscale Scores for those with Low and High Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. The groups were split based on a median split (17.00) into the two groups.
BNSS Low AAA: *N*=20, *r*=-.477*, p<0.10.* BNSS High AAA: *N*=17, *r*=.387*, p<0.10.*

Figure 6

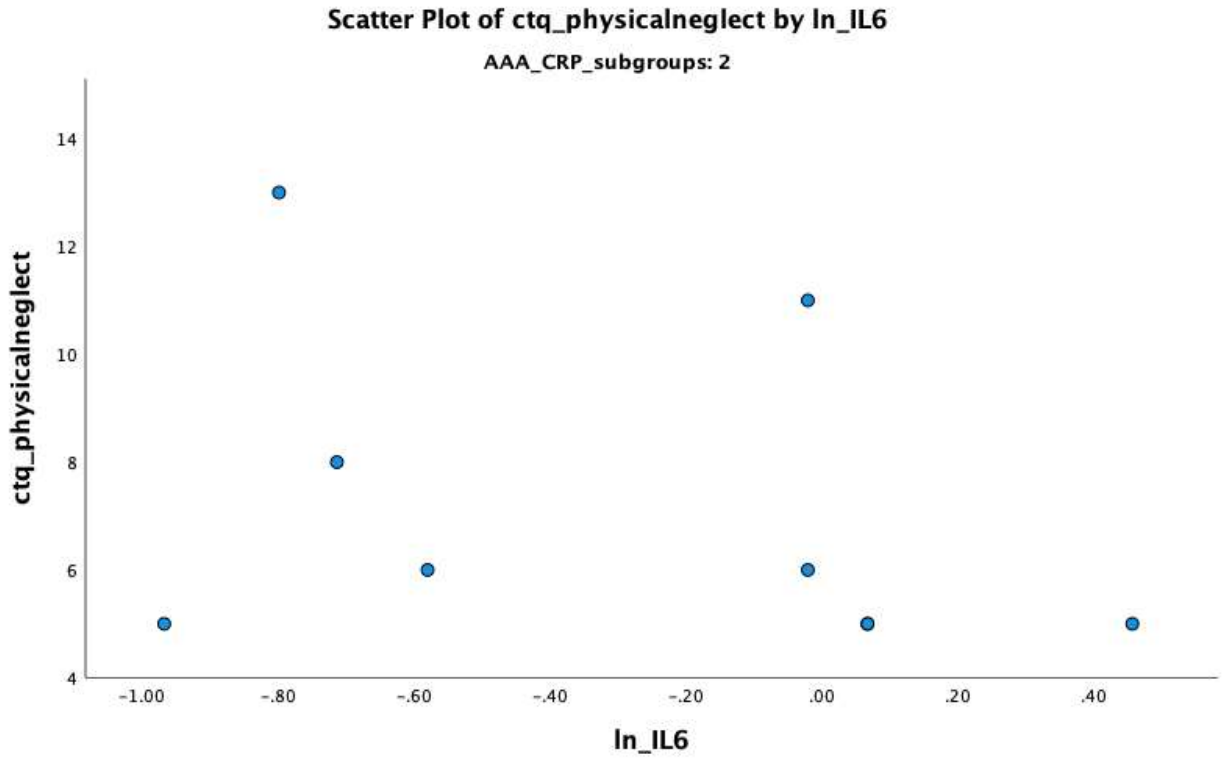
Comparison of the Relationship between Interleukin-6 (IL-6) and Childhood Trauma Questionnaire Physical Neglect Subscale Scores for those with Low Inflammation (as indexed by C-Reactive Protein) and Low Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. *N*=11, *r*=.554, *p>0.10.*

Figure 7

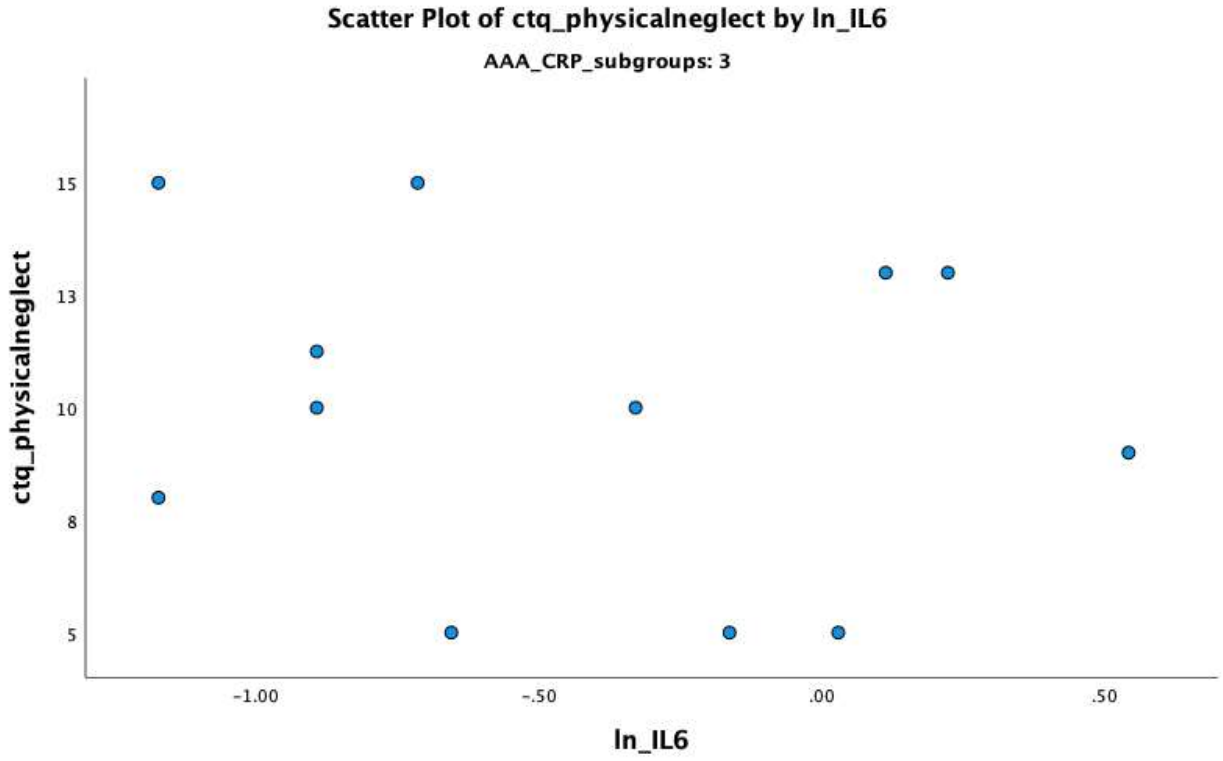
Comparison of the Relationship between Interleukin-6 (IL-6) and Childhood Trauma Questionnaire Physical Neglect Subscale Scores for those with High Inflammation (as indexed by C-Reactive Protein) and Low Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. *N*=12, *r*=-.174, *p>0.10.*

Figure 7

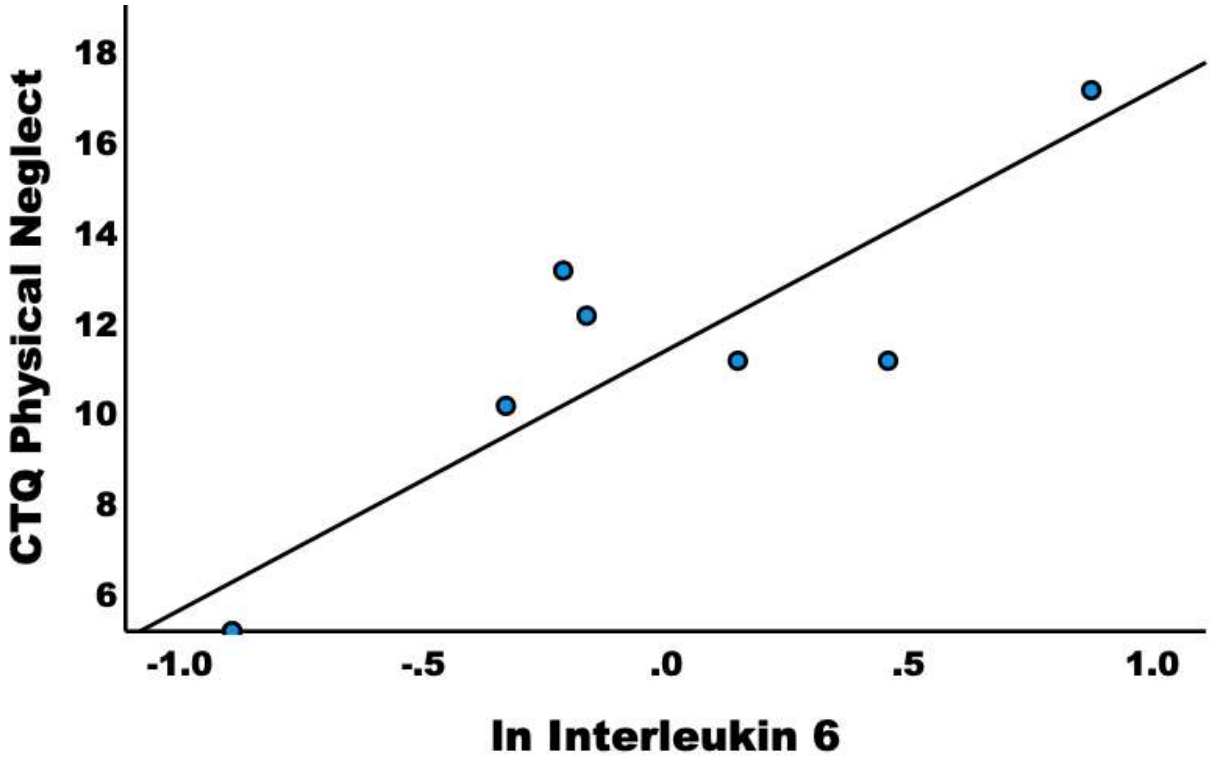
Comparison of the Relationship between Interleukin-6 (IL-6) and Childhood Trauma Questionnaire Physical Neglect Subscale Scores for those with Low Inflammation (as indexed by C-Reactive Protein) and High Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. *N*=9, *r*=-.481, *p>0.10.*

Figure 7

Comparison of the Relationship between Interleukin-6 (IL-6) and Childhood Trauma Questionnaire Physical Neglect Subscale Scores for those with High Inflammation (as indexed by C-Reactive Protein) and High Deficits in Motivated Behaviors (as indexed by the Brief Negative Symptom Scale, BNSS)



Note. *N*=8, *r*=.776, *p*<0.05.