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Traumagenics: At the intersect of childhood trauma, immunity and psychosis

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ABSTRACT

Early childhood trauma, including physical, sexual or emotional abuse, neglect, harm or threat of harm, is associated with adulthood dysregulation of the immune system. Trauma can induce chronic immune system activation. Associations between a chronic pro-inflammatory state and schizophrenia are an enduring finding of psychiatry, with elevated cytokine concentrations correlated with psychotic symptom severity. Most importantly, persons with schizophrenia and a history of childhood trauma demonstrate increased cytokine levels. Specific types of childhood trauma can also differentially impact the expression of unique immune markers. This study tested the hypotheses that levels of adverse childhood experiences (ACEs) would be associated with levels of peripheral immune activity assessed by *IL6, IFNG, CXCL10, IRF1, STAT1* and *TLR4* mRNA expression, and that there would be an association between ACEs and psychosis along a continuum from non-clinical controls (NCC) to psychotic disorders such as schizophrenia. These hypotheses were tested in 20 schizophrenia, 20 NCC. We found correlations between ACEs scores and immune markers, specifically *IL6*. We also found a positive association between ACEs and positive symptoms. Childhood trauma, through its effects on *IL6*, may be a risk factor for schizophrenia.

1. Introduction

Early childhood trauma, defined as physical or sexual abuse, neglect, emotional abuse, harm or threat of harm prior to the age of 18, has long been associated with increased risk of developing psychosis (Bernstein et al., 2003). This association has been found to take the form of a dose-response relationship (Shevlin et al., 2008; Varese et al., 2012). For example, exposure to more than four childhood traumatic events has been found to result in a 10 times greater risk of developing schizophrenia (Alvarez et al., 2015). Some studies have reported a relationship between type of childhood traumatic event (i.e. sexual and/or physical abuse) and specific symptoms of psychosis (i.e. hallucinations, delusions) (Bentall et al., 2012; Sitko et al., 2014; Muenzenmaier et al., 2015). While other research did not find specific childhood traumatic events relating to specific psychotic symptoms (Longden et al., 2016; van Nierop et al., 2015).

There are several hypotheses linking trauma and psychosis. Childhood trauma, in conjunction with genetic vulnerability and/or other environmental factors, such as infection and socioeconomic stressors, leads to changes in gene expression that may contribute to later development of psychosis (Babenko et al., 2015; Brietzke et al., 2012). Alternately or in addition, psychological mechanisms such as affect regulation, intrusive trauma memories, cognitive biases, dissociative mechanisms and depression may mediate the relationship between adversity and onset (Hardy et al., 2016; Pearce et al., 2017). These long-term modifications to the transcriptome are likely mediated by epigenetic mechanisms such as histone and DNA methylation.

The literature supports a significant association between childhood trauma and adulthood dysregulation of the immune system (Danese et al., 2009). Trauma is able to induce chronic immune system activation and hyper-reactivity, thus impacting brain development and neuronal connections (Danese and Baldwin, 2017; Molina, 2005; Radhakrishnan et al., 2017). Furthermore, the immune system is associated with the pathoetiology of psychosis and mood and anxiety disorders, and administration of anti-inflammatory drugs is shown to be conducive to decreases in symptom presentation (Khandaker et al.,

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2015; Mondelli and Howes, 2014; Rosenblat et al., 2014). Associations between a chronic pro-inflammatory state and schizophrenia have been one of the more enduring findings of psychiatry (Brodin et al., 2015; Chase et al., 2016), with many studies demonstrating elevated cytokine concentrations with increased psychotic symptom severity (Goldsmith et al., 2016). Most importantly, persons with schizophrenia who have a history of childhood trauma demonstrate increased cytokine levels (Dennison et al., 2012). Specific types of childhood trauma (sexual, physical or emotional abuse) can also differentially impact expression of unique immunity markers (Baumeister et al., 2016).

Two primary intracellular signaling systems mediating immune responses are the NF-κB and JAK-STAT1 pathways (Schroder et al., 2006). Activation of the NF-κB pathway in response to ligation of the pathogen- and damage-sensing receptor TLR4, leads to secretion of proinflammatory cytokines such as IL6. The JAK-STAT1 pathway is activated predominantly by interferons, and interferon gamma (IFNγ) increases expression of genes including *CXCL10, IRF1, STAT1* and *TLR4* (Bosisio et al., 2002; Satoh and Tabunoki, 2013). While there is overlap of genes and biological processes induced by these two pathways, we have recently demonstrated an increase in *IL6* and a decrease in *IFNG, CXCL10, IRF1, STAT1* and *TLR4* gene expression in peripheral blood mononuclear cells (PBMCs) from a subset of participants with psychosis, indicating a dichotomy between these two signaling systems (Chase et al., 2016; Melbourne et al., 2018). Mechanisms governing this distinction are currently unclear. The genes were selected because they underlie inflammation, a specific response by the innate immune system when it senses pathogens or damage, and that can become chronic due to repeated stimuli or failure to adequately resolve. However, these immune effectors genes also mediate other aspects of innate and adaptive immunity, in a context and cell type dependent manner. Building on this rich body of literature, this exploratory study aims to examine the relationship of trauma, immunity and psychosis by testing the following hypotheses:

1 Adverse childhood experiences (ACEs) scores and *IL6* mRNA expression level would be higher in participants with schizophrenia than in non-clinical controls (NCC), whereas expression of *IFNG, CXCL10, IRF1, STAT1* and *TLR4* mRNA would be decreased in participants with schizophrenia compared to NCC.
2 Levels of ACEs would be associated with levels of peripheral immune activity along a continuum in participants from NCC to psychotic disorders such as schizophrenia as assessed by *IL6, IFNG, CXCL10, IRF1, STAT1* and *TLR4* mRNA expression.
3 There would be an association between specific types of adverse childhood events (i.e. abuse, neglect, dysfunction) and psychosis (PANSS positive subscale) along a continuum in participants from NCC to participants with a diagnosis of schizophrenia.

2. Methods

2.1. Participants

The sample included 40 participants: 20 diagnosed with schizophrenia and 20 with no current or previous psychiatric history. Participants with schizophrenia were assessed by experienced diagnosticians (MD or PhD) using the Structured Clinical Interview for DSM Disorders (SCID-IV) interview (First et al., 2002). Demographic characteristics, age of illness onset, duration of untreated psychosis (DUP), and duration of illness were obtained per self-report. DUP was defined as the number of years between onset of psychosis-related symptoms and initiation of antipsychotic medication, and duration of illness was defined as the number of years between onset of illness and current age. Antipsychotic use for participants with schizophrenia was converted to chlorpromazine equivalents (CPZE) (Gardner et al., 2010; Danivas and Venkatasubramanian, 2013). Participant demographics are reported in Table 1.

The clinical sample was selected from a large urban university medical center that included referrals from community treatment facilities. The NCC sample was selected from the surrounding urban community. The study was approved by University of Illinois at Chicago Internal Review Board (IRB2012-0113). All participants gave signed written consent prior to initiation of any research procedures. Inclusion criteria were that the participants be between the ages of 21–60 years, in good physical health (with no reported infections or autoimmune diseases) and met diagnostic criteria for schizophrenia (clinical sample) or participants who did not meet SCID-IVtr criteria for a major psychiatric disorder (non-clinical controls; NCC). Exclusion criteria included current substance dependence, current pregnancy, seizure disorders or neurological conditions.

The clinical group (n = 20) consisted of participants who met SCID DSM-IVtr diagnostic criteria for schizophrenia and who were experiencing present state psychosis. The mean age onset of illness was 22 years with a mean DUP of three years and a mean duration of illness of 16 years. Within the clinical sample all participants reported actively taking antipsychotic medications, of which 18 (90%) were prescribed atypical antipsychotic medications and two (10%) participants were prescribed typical antipsychotic medications.

2.2. Measures

2.2.1. Adverse Childhood Experiences (ACEs)

Childhood adversity/trauma was assessed using the Adverse Childhood Experiences (ACEs) questionnaire (Felitti et al., 1998). This is a ten-item questionnaire that assesses experiences related to abuse, neglect and household dysfunction occurring prior to the age of 18. All scores were binary (yes or no). From these, a dichotomous variable was created to reflect accumulative exposure and three subscales: 1) ACEs abuse (emotional, physical and sexual abuse); 2) ACEs neglect (emotional and physical neglect); and 3) ACEs household dysfunction (parental separation / divorce, violence against mother, household substance abuse, household mental illness and incarceration of household member) (Cheong et al., 2017). Total ACEs scores can range from 0 to 10, with higher scores indicating a greater number of ACEs. Internal reliability Cronbach's alpha of ACEs scores in this study were 0.79 for both ACE abuse and neglect, 0.76 for ACE dysfunction and 0.80 for ACEs total score.

2.2.2. Positive and Negative Syndrome Scale (PANSS)

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). PANSS items were scored along a continuum of severity between 1 (asymptomatic) to 7 (extreme symptom severity). Analysis was conducted via data reduction strategies guided by prior empirical studies of symptom domains assessed by the PANSS. For the purposes of this research we focused specifically on PANSS Positive symptom subscale (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility). Internal reliability of PANSS Positive symptom subscale, as calculated through Cronbach's alpha, was 0.94 in this study.

2.3. Immune markers

Blood samples given by participants were assessed for expression levels of *IL6, IFNG, CXCL10, IRF1, STAT1* and *TLR4* mRNA using quantitative real-time PCR (RT-PCR).

2.3.1. Peripheral blood mononuclear cell extraction

A blood sample was obtained by sterile venipuncture into a 0.5 M EDTA anticoagulant filled tube. Peripheral blood mononuclear cells (PBMC) were extracted utilizing Ficoll–Paque® method (GE Healthcare Life Sciences) (Jayaraman et al., 1999). Subsequent washing buffy interlayer was performed using Hanks Balanced Salt Solution (HBSS;

Table 1
Demographic and clinical characteristics of sample (n = 40).

	Control (n = 20)		Schizophrenia (n = 20)		Group difference
Sex					*Fisher's Exact test* p = 1.00 (n.s.)
Male	10 (50%)		10 (50%)		
Female	10 (50%)		10 (50%)		
Race					$\chi 2(3) = 5.05$, $p = 0.17$ (n.s.)
African American	10 (50%)		16 (80%)		
Asian	3 (15%)		1 (5%)		
Caucasian	5 (25%)		1 (5%)		
Hispanic	2 (10%)		2 (10%)		
	Mean	**SD**	**Mean**	**SD**	
Age	38.15	13.52	37.85	12.38	$t_{38} = 0.07$, $p = 0.94$ (n.s.)
BMI	27.87	6.53	34.89	7.64	$t_{38} = -3.12$, $p = 0.003$
Smoking	1.16	0.37	1.35	0.59	$t_{37} = -1.21$, $p = 0.23$ (n.s.)
Age at onset of illness	~	~	22.47	8.70	
Duration of untreated psychosis	~	~	2.74	7.14	
Duration of illness	~	~	15.84	14.31	
CPZE	~	~	416.67	315.29	

SD = Standard deviation. Age, age at onset, duration of untreated psychosis and duration of illness are all given in years.

Gibco 14170-161) to remove remaining platelets, plasma or other contaminants. PBMC samples were pelleted at 2000 RPM for ten minutes at 10 °C and frozen in TRIzol reagent (Life Technologies) at −80 °C until mRNA extraction (Chase et al., 2016).

2.3.2. RNA extraction, reverse transcription and real-time PCR

Total RNA was isolated using TRIzol reagent and treated with DNase (Ambion/Life Technologies AM1906) after extraction. Only total RNA extracts with an OD260/OD280 ratio above 1.96, indicating relatively pure RNA, were processed for RT-PCR, the remainder undergoing re-extraction using standard phenol-chloroform extraction protocol. Total RNA was used to prepare cDNA via Applied Biosystems High Capacity cDNA Reverse Transcription Kit (4368814). For detection and measurement of expression, Fermentas Maxima SYBR Green/ROX qPCR Master Mix (K0222) was used. PCR mixtures were run on Thermo Scientific PikoReal real-time PCR System using the following conditions: 95 °C for 10 min, followed by 40 cycles of 95 °C for 30 s, 60 °C for one minute and 72 °C for one minute. Cycle threshold (CT) value was used for relative quantification, and values were normalized to three housekeeping genes, *GAPDH, TFRC* and *ACTB* for *IL6*, and *GAPDH* and *ACTB* for the remaining genes (Chase et al., 2016) using a geometric mean, and run in triplicate (Mannhalter et al., 2000; Vandesompele et al., 2002).

2.4. Data analysis

All statistical analyses were conducted using SPSS version 24.0. Between-group differences in demographics were analyzed using chi-squared tests (including Fisher's exact tests), and independent sample *t*-tests. Effect of clinical status (schizophrenia, non-clinical population) on mRNA expression of *IL6, IFNG, CXCL10, IRF1, STAT1* and *TLR4* were first to be assessed using multivariate analysis of variance (MANOVA). If found to be significant, this result was to be followed up by independent sample *t*-tests comparing immune measures between the two groups. Bonferroni corrections for multiple testing were applied. Pearson's bivariate correlations with bootstrapping at 1000 iterations were conducted to determine associations between trauma (as measured by ACEs), immunity (as measured by mRNA expression) and psychopathology (as measured by PANSS positive symptom subscale). Biological measure scores that were not normally distributed were converted to log transformation scores and the log transformed scores were applied to subsequent analysis. Although there are demographic, clinical and *IL6* data on all 40 participants; there are missing data for the remaining genes due to sample availability. Type II statistical errors were minimized in this exploratory study, so as to better characterize potential associations guiding future research studies. Given this, our results are to be interpreted with caution and viewed as hypotheses for further investigation (Armstrong, 2014).

3. Results

3.1. Descriptive characteristics

Group comparisons of demographic characteristics found no significant differences in sex, race or age between clinical and NCC groups (Table 1). As antipsychotic usage is known to affect immune parameters (Maes et al., 1997), to test for confounding effects between antipsychotic usage and immune biomarkers, we examined correlations between CPZE level and expression levels. We found no significant correlation between CPZE level and *IL6* ($r = -0.008$, $p = 0.98$), *CXCL10* ($r = -0.295$, $p = 0.27$), *STAT1* ($r = -0.248$, $p = 0.35$), or *TLR4* ($r = 0.030$, $p = 0.91$). However, there was a negative correlation between CPZ and *IFNG* ($r = -0.601$, $p = 0.02$) and *IRF1* ($r = -0.510$, $p = 0.04$). We also examined correlations between BMI and expression in immune biomarkers and found a negative correlation between BMI and *IFNG* ($r = -0.429$, $p = 0.01$). There was no significant difference between BMI and *IL6* ($r = 0.282$, $p = 0.11$), *CXCL10* ($r = -0.052$, $p = 0.78$), *IRF1* ($r = -0.152$, $p = 0.40$), *STAT1* ($r = -0.068$, $p = 0.71$), or *TLR4* ($r = 0.067$, $p = 0.71$). There also was no significant group difference in smoking nor were there any significant correlation between smoking and any of the biomarker expression levels. Due to these findings, a multiple regression analysis was used to test if BMI significantly predicted participants' *IFNG* expression. The results of the regression indicated the two predictors, BMI and diagnosis, explained 21.3% of the variance ($R^2 = 0.23$, $F(1,36) = 11.03$, $p < 0.002$). It was found that only diagnosis significantly predicted decreased levels on *IFNG* expression ($\beta = -1.07$, $p < 0.002$). We also found there were no significant associations between age and gender with immune biomarkers. Given that no significant relations were found, age, gender, smoking and BMI were not controlled for in our further analyses.

3.2. Group differences in ACEs scores and immune gene expression

MANOVA found an effect of group (schizophrenia vs NCC) on *IL6, IFNG, CXCL10, IRF1, STAT1* and *TLR4* mRNA expression, $F(6, 26) = 4.65$, $p < 0.002$; Wilks $\Lambda = 0.483$, partial $\eta^2 = 0.52$. Follow-up independent sample *t*-tests revealed that *IL6* was significantly higher in participants with schizophrenia compared to NCC, and *IFNG, CXCL10, IRF1,* or *STAT1* were significantly lower in participants with schizophrenia when compared to NCC, and there was no significant difference between groups in *TLR4* (Table 2; Fig. 1a). However, not all of these differences withstood corrections for multiple testing using Bonferroni

Table 2
Diagnostic differences in ACEs scores and inflammatory pathway gene expression.

	Control (n = 20)			Schizophrenia (n = 20)			Group difference
	Range	Mean	SD	Range	Mean	SD	
Adverse Childhood Events (ACEs)							
ACEs total score	0–10	3.45	2.95	3–10	5.70	2.11	t_{38} = 2.78, p = 0.008*, Cohen's d = 0.88
ACEs -abuse	0–4	1.45	1.47	1–4	2.50	0.76	t_{38} = 2.84, p = 0.008*, Cohen's d = 0.90
ACEs -neglect	0–2	0.80	0.89	0–2	1.30	0.86	t_{38} = 1.80, p = 0.08, Cohen's d = 0.57
ACEs -dysfunction	0–4	1.20	1.51	1–4	1.90	0.91	t_{38} = 2.13, p = 0.04, Cohen's d = 0.67
Immunity bio-markers							
IL6	~	1.09	0.57	~	1.68	0.49	t_{38} = −3.52, p = 0.001**, Cohen's d = 1.11
IFNG	~	4.33	0.53	~	3.25	1.27	t_{36} = 3.45, p = 0.002**, Cohen's d = 1.11
CXCL10	~	2.82	0.60	~	2.31	0.66	t_{34} = 2.26, p = 0.03, Cohen's d = 0.81
IRF1	~	2.35	0.50	~	1.64	0.55	t_{35} = 4.16, p < 0.000**, Cohen's d = 1.35
STAT1	~	1.80	0.57	~	1.33	0.54	t_{35} = 2.55, p = 0.02, Cohen's d = 0.85
TLR4	~	2.38	0.53	~	2.12	0.37	t_{35} = 1.80, p = 0.08, Cohen's d = 0.57

SD = Standard Deviation; *Significant after Bonferroni correction to alpha for multiple testing, p' = 0.05 /4 = 0.01. ** Significant after Bonferroni correction to alpha for multiple testing, p' = 0.05 /6 = 0.008.

correction at alpha of 0.008 on this small exploratory sample. A diagnostic difference between *IL6, IFNG* and *IRF1* remained significant after Bonferroni correction.

We next conducted a MANOVA to examine the effect of group (schizophrenia vs NCC) on ACEs total scores including ACEs subscale scores (ACEs-abuse, ACEs-neglect and ACEs-dysfunction) and found an effect of group (schizophrenia vs NCC), $F(3, 36) = 2.65$, $p < 0.05$; Wilks $\Lambda = 0.819$, partial $\eta^2 = 0.18$. Follow-up independent sample t-tests revealed that ACEs total score, ACEs-abuse, and ACEs-dysfunction subscores were significantly higher in participants with schizophrenia compared to NCC (Table 2; Fig. 1b). There was no significant difference between groups in ACEs-neglect scores. Diagnostic difference between ACEs total score and ACEs-abuse remained significant after a Bonferroni correction was applied at alpha of 0.01.

3.3. Associations between adverse childhood experiences and immune marker gene expression

Associations between cumulative ACEs scores and immune markers in the overall sample (NCC and schizophrenia combined) are presented in Table 3; Fig. 2a. Total ACEs scores positively correlated with levels of peripheral *IL6* mRNA. Further analysis found that all three ACEs scores subscale (ACEs-abuse, ACEs-neglect and ACEs-dysfunction) positively correlated with *IL6* mRNA expression (Supplemental Figure 1). Total ACEs scores were negatively correlated with levels of peripheral *IRF1* and *TLR4* mRNA. Further mRNA expression analysis found that all three ACEs score subscales were negatively correlated with *IRF1* (Supplemental Figure 2). Additionally, ACEs-neglect were negatively correlated with *TLR4* mRNA. There were no significant associations between total ACEs scores (or any ACEs score subscales) and *IFNG, CXCL10* and *STAT1* mRNA levels.

As shown in Fig. 3, correlations between total ACEs score and peripheral *IL6* mRNA levels was found in participants regardless of clinical status in both participants diagnosed with schizophrenia (r = 0.809, p = 0.000) and NCC (r = 0.622, p = 0.02). In contrast, there was no significant association between total ACEs score and *IFNG, CCXL10,* and *STAT1* mRNA levels within schizophrenia or NCC groups alone. Lastly, associations between total ACEs score and both *IRF1* (r = −0.611, p = 0.02) and *TLR4* (r = −0.613, p = 0.02) levels were only significant in the NCC group.

3.4. Associations between immune markers and PANSS positive scores

The combine sample showed a positive correlation between *IL6* and PANSS positive scores, with higher mRNA levels corresponding to higher levels of PANSS positive scores (Table 3). We also demonstrated negative correlations between *IFNG, IRF1, STAT1, TLR4* mRNA levels and PANSS positive scores, in that as mRNA levels decreased, PANSS positive scores increased. There was no association between *CXCL10* and PANSS positive scores. However, when this association was examined within schizophrenia alone showed no association between *IL6* (r = 0.063, p = 0.80), *IFNG* (r = −0.074, p = 0.77), *CXCL10* (r = 0.141, p = 0.56) and *IRF1* (r = 0.119, p = 0.60), *STAT1* (r = 0.091, p = 0.72), *TLR4* (r = 0.090, p = 0.71) and PANSS positive scores.

3.5. Associations between adverse childhood experiences and positive symptom severity

As shown in Table 3, within the total combined sample (schizophrenia and NCC) there was a positive correlation between PANSS positive symptoms and ACEs total scores, including ACEs abuse, ACEs-neglect and ACEs-dysfunction. However, when this association was examined within schizophrenia alone there was no association between PANSS positive symptoms and ACEs total scores (r = 0.123, p = 0.53), ACEs-abuse (r = 0.108, p = 0.62), ACEs-neglect (r = 0.080, p = 0.74) and ACEs-dysfunction (r = 0.173, p = 0.48).

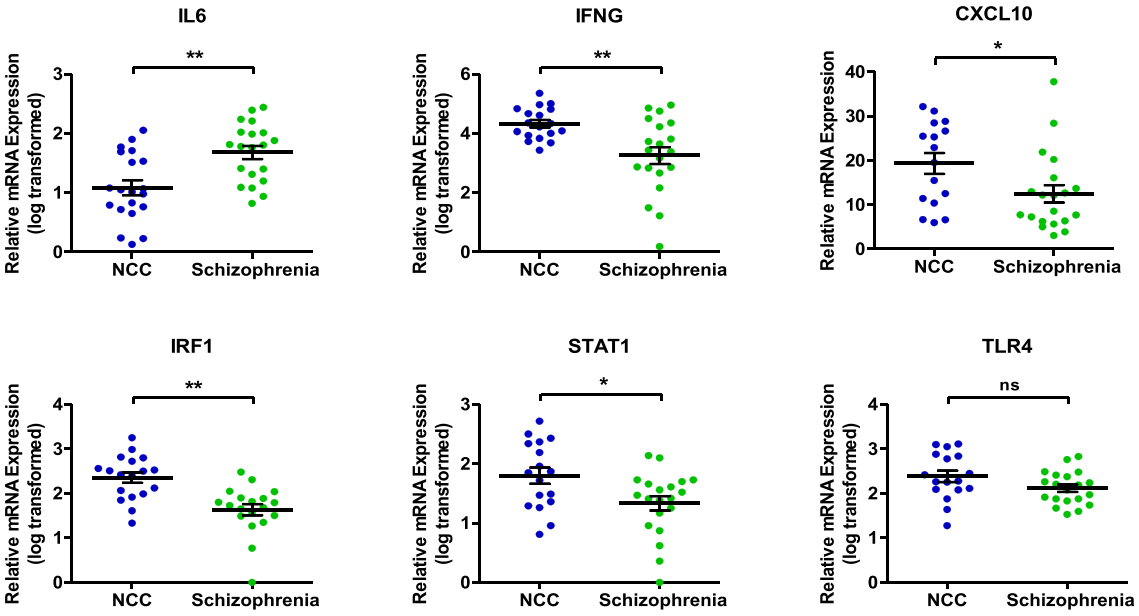
4. Discussion

Adverse childhood events have been known to be associated with alterations in immune markers, psychiatric symptoms, adult social, emotional and cognitive impairments, high-risk behaviors, poor physical health, and early death (Bailey et al., 2018; Danese and Baldwin, 2017; Felitti et al., 1998; Misiak et al., 2017;).

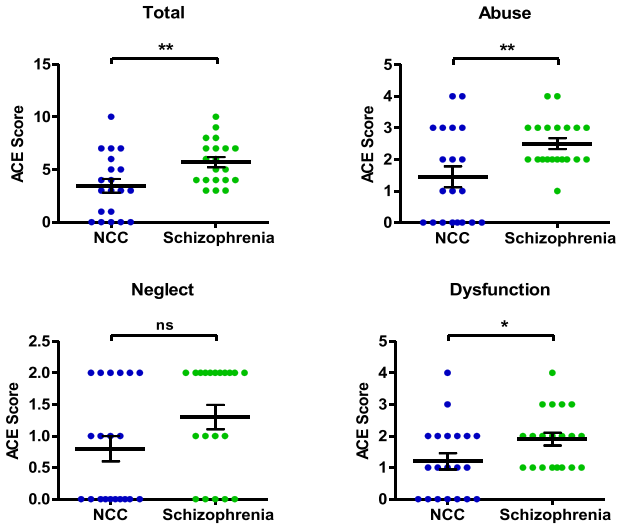
This study examined the association of childhood adversity/trauma (traumatic events prior to the age of 18), immunity and psychosis along a continuum from NCC to psychotic disorders such as schizophrenia. Our findings that adverse childhood events are more prevalent in participants with schizophrenia, particularly overall prevalence and experiences of childhood sexual or physical abuse when compared to a NCC sample is consistent with previous research. We also demonstrated that exposure to childhood traumatic life events are associated with both specific peripheral immune biomarkers (*IL6, IRF1* and *TLR4*) and psychosis (PANSS positive subscale) in the total sample. Additionally, a positive correlation between cumulative childhood adverse events and *IL6* mRNA levels was found in all participants, whereas *IRF1* and *TLR4* was only significant in the NCC group. Therefore, childhood trauma, through its effects on *IL6* levels, may be a risk factor for schizophrenia in general.

4.1. Childhood trauma and immunity

It is well established that acute and chronic stressors can have a



Non-clinical control (NCC); * Significant at $p \leq 0.05$; ** Significant after Bonferroni correction to alpha for multiple testing, p'= 0.05 /6 =0.008



* Significant at $p \leq 0.05$; **Significant after Bonferroni correction to alpha for multiple testing, p' = 0.05 /4 = 0.01.

Fig. 1. (a) Relative mRNA expression of each gene displayed by diagnostic category. Non-clinical control (NCC); * Significant at $p \leq 0.05$; ** Significant after Bonferroni correction to alpha for multiple testing, $p' = 0.05/6 = 0.008$. (b) Adverse childhood events (total exposure, abuse, neglect, dysfunction) by diagnostic category. * Significant at $p \leq 0.05$; **Significant after Bonferroni correction to alpha for multiple testing, $p' = 0.05/4 = 0.01$.

long-lasting impact on immune function. These effects are thought to be mediated by changes to HPA axis function and sympathetic nervous system (SNS) outflow, both of which influence peripheral immune cell differentiation and phenotype (Miller et al., 2009; Weber et al., 2016). Rodent models indicate that the changes to immune activity are dependent on the nature of the stressor (Weber et al., 2016; Zhang et al., 2008). In the repeated social defeat model, pro-inflammatory monocytes are actively recruited to the brain and appear to influence behavior. Similar mechanisms are proposed to contribute to changes in immune parameters following chronic social stress in humans, termed 'conserved transcriptional response to adversity' (CTRA; (Powell et al., 2013)). In some studies that investigate the transcriptional signature in chronically stressed humans, an increased NF-κB mediated signature and a decreased type I IFN/IRF1 signature is noted, though the mechanism underlying this distinction is unknown (Cole et al., 2007, 2015). However, only one study focused on early life stressors, using early life socioeconomic status (Miller et al., 2009). While the authors noted an increased NF-κB promoter binding, none of the genes measured for this study were amongst those differentially expressed using genome-wide analysis in adults who had experienced high early life socioeconomic stressors. Our data support a distinction between NF-κB (*IL6*) and IFN (*IRF1* and *TLR4*) mediated transcriptional alterations in subjects who have experienced early life stress. We focus specifically on early life adversity/trauma, and further demonstrate that both early life adversity/trauma and immune biomarkers are associated with psychosis.

Table 3
ACEs, Immunity biomarkers and PANSS clinical subscales. Pearson's *r* correlations (95% confidence intervals) between ACEs scores, immunity biomarkers and PANSS clinical subscales.

ACES, Immunity biomarkers and PANSS clinical subscales	ACEs total scores	ACEs-abuse subscale	ACEs-neglect subscale	ACEs-dysfunction subscale	PANSS positive subscale
IL6	**0.789 [0.624, 0.894]**	**0.648 [0.343, 0.847]**	**0.634 [0.410, 0.801]**	**0.687 [0.502, 0.828]**	**0.495 [0.197, 0.724]**
	***p* = 0.000**	***p* = 0.000**	***p* = 0.000**	***p* = 0.000**	***p* = 0.003**
IFNG	−0.184 [−0.406, 0.110]	−0.159 [−0.403, 0.110]	−0.111 [−0.397, 0.218]	−0.184 [−0.418, 0.102]	**−0.455 [−0.684, −0.246]**
	p = 0.305	*p* = 0.378	*p* = 0.537	*p* = 0.305	***p* = 0.008**
CXCL10	−0.221 [−0.520, 0.101]	−0.267 [−0.595, 0.076]	0.043 [−0.348, 0.376]	−0.284 [−0.535, 0.001]	−0.283 [−0.594, 0.023]
	p = 0.217	*p* = 0.134	*p* = 0.811	*p* = 0.110	*p* = 0.110
IRF1	**−0.601 [−0.751, −0.393]**	**−0.516 [−0.744, −0.209]**	**−0.405 [−0.613, −0.141]**	**−0.565 [−0.746, −0.369]**	**−0.448 [−0.654, −0.207]**
	***p* = 0.000**	***p* = 0.002**	***p* = 0.019**	***p* = 0.001**	***p* = 0.009**
STAT1	−0.159 [−0.422, 0.177]	−0.042 [−0.406, 0.340]	−0.042 [−0.310, 0.326]	−0.328 [−0.588, −0.056]	−0.309 [−0.556, −0.004]
	p = 0.377	*p* = 0.819	*p* = 0.818	*p* = 0.063	*p* = 0.080
TLR4	**−0.395 [−0.622, −0.048]**	−0.331 [−0.618, 0.028]	**−0.383 [−0.609, −0.081]**	−0.277 [−0.510, −0.047]	**−0.381 [−0.622, −0.068]**
	***p* = 0.023**	*p* = 0.060	***p* = 0.028**	*p* = 0.119	***p* = 0.029**
PANSS Positive Subscale	**0.526 [0.240, 0.727]**	**0.515 [0.202, 0.759]**	**0.397 [0.030, 0.684]**	**0.377 [0.040, 0.618]**	~
	***p* = 0.002**	***p* = 0.002**	***p* = 0.022**	***p* = 0.030**	

Confidence intervals calculated using 1000 bootstrapped samples. $p < 0.05$ are bolded.

4.1.2. Childhood trauma, immunity and psychopathology

Associations between trauma and experiences of psychosis and psychotic disorders is longstanding (Clark, 1932; MacDougall, 1939). To date, there is emerging evidence suggesting that early childhood adversity is a causal risk factor in developing psychosis and psychotic disorders along the psychosis spectrum, from NCC to psychotic disorders such as schizophrenia (Kelleher et al., 2013; Murray, 2017; Trauelsen et al., 2015). In a recent meta-analysis Bailey et al. (2018) reported that occurrence of childhood trauma and sexual abuse are associated with the severity of positive symptoms. In keeping with previous research, our findings show that the prevalence and severity of adverse/traumatic childhood events in the total sample are associated with increased clinical symptoms of psychosis (Bebbington et al., 2004; Janssen et al., 2004; Rosen et al., 2017; Spauwen et al., 2006).

As stated earlier, trauma can have a lasting impact on gene transcription that may underlie global, systems-level biological changes. There is a growing body of literature that highlights the relationship between childhood trauma and enduring alterations to epigenetic parameters and gene transcription (Klengel and Binder, 2015). For example, a recent study by Dunn et al. (2018) found a relationship between age of exposure to adverse events and alterations in DNA methylation. Additionally, recent research has also demonstrated a relationship between adverse childhood experience and chronic immune alteration and increase in proinflammatory cytokines which could lead to greater susceptibility for developing psychiatric symptoms, including psychosis (Moreira et al., 2018). In sum, it is well documented that adverse childhood events are a risk factor for psychosis (Alvarez et al., 2011; Tomassi and Tosato, 2017; Varese et al., 2012).

Our study demonstrates that participants diagnosed with schizophrenia have experienced occurrence of adverse childhood events and specifically occurrence of abuse (sexual and physical) to a greater degree compared to NCC. Furthermore, group differences for this study in which gene expression of *IL6* is elevated, and expression of *IRF1* is suppressed in participants diagnosed with schizophrenia are consistent with expression data from a larger sample (Chase et al., 2016; Melbourne et al., 2018). Regarding immune activity and psychosis in the combined total sample, there were positive correlations between psychosis and *IL6*, with higher mRNA levels corresponding to higher levels of positive symptom presentation, an effect that is in keeping with the literature (Chase et al., 2016; Upthegrove et al., 2014), and negative correlations between psychosis and *IFNG, IRF1, STAT1* and *TLR4* expression levels, with lower mRNA levels corresponding to higher levels of positive symptoms presentation.

4.2. Continuum of ACEs, immunity and psychosis

This heterogeneous sample of NCC and participants diagnosed with schizophrenia were analyzed along a continuum of exposure to trauma and experiences of psychosis since trauma, immunity and psychosis exist in the general population along a continuum. As trauma is not a diagnostic category an attempt to measure its coordinates would require a collection of subjects that were enriched for this experience. This approach is strengthened by the absence of the prevalence or severity of trauma as part of the inclusion criteria. The inclusion of non-psychotic participants would also protect against an artificial correlation that could occur in participants with psychosis as trauma is known to be associated with psychosis. By doing such we were also able to measure immunity along this continuum. We also report findings based on diagnostic specificity to delineate group differences of ACEs, immunity and psychosis at a specific point in time. A recent publication by Loewy et al. (2018) evaluated the potential causative effect of trauma in participants with high risk for psychosis while also reporting diagnostic group differences. The benefits of such an approach allows for the implications of findings to reflect the complex heterogeneity that exists within the general population while also recording potential signature clinical and biological phenotypes and/or diagnostic specificity at a

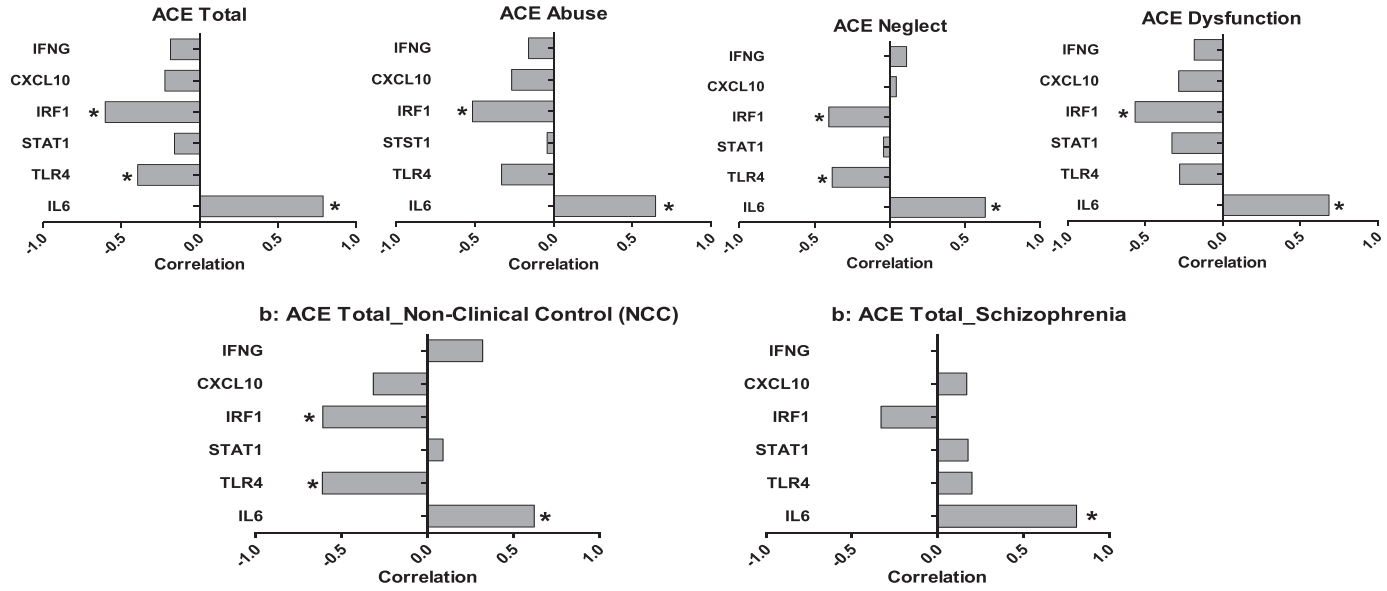


Fig. 2. (a) Full Sample: Adverse childhood events (total exposure, abuse, neglect, dysfunction) and immune-related gene expression. (b) Adverse childhood events (ACEs total scores) and immunity biomarkers in Non-Clinical Control (NCC) and in the Schizophrenia group.

specific point in time. Although we did not find a significant association in this schizophrenia cohort, data from the larger sample does demonstrate an association between gene expression and psychosis (Chase et al., 2016; Melbourne et al., 2018). Thus data related to trauma, immune function and psychosis requires an interpretation that includes both continuum population based and diagnostic categorical paradigms.

4.3. Clinical implications

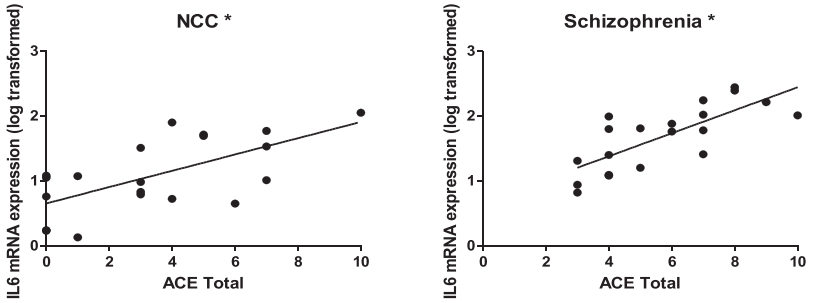
This type of biochemistry has significant implications for prevention, identification, and intervention from both a pharmacological as well as psychotherapeutic approach and can also explains findings of a strong relationship between trauma (and other adverse experiences) and chronic immune alterations (Sharma et al., 2012; van Os et al., 2010). If the impact of trauma on immune function in adulthood does indeed contribute to psychopathology, an improved understanding of this relationship in persons with psychosis may lead to treatment options that target specific immune parameters (Melbourne et al., 2017; Miller et al., 2011).

Other clinical implications of these findings include increased emphasis in establishing more comprehensive screening of early trauma, such as the Psychotic Symptoms Early Trauma Checklist (CAP) in persons that present with psychotic symptoms regardless of age or diagnostic status (Coughlan and Cannon, 2017). Conversely, children who report traumatic events should be screened and followed up for the emergence of psychotic symptoms. Additionally, measures such as the Maastricht Interview for Voice Hearers that are structured to evaluate the experience of a specific symptom such as hearing voices and trauma history are designed to evaluate the association of specific symptoms such as voices and trauma should be included in the evaluation process (Corstens et al., 2008).

In addition to more comprehensive evaluations there is a need to further develop clinical interventions such as trauma informed care for persons with psychosis that could be tailored for specific types or clusters of childhood trauma (i.e. sexual, physical, dysfunction) and specific symptoms or symptom clusters (hallucinations, delusions, negative symptoms). Other trauma-based therapies such as cognitive-oriented trauma-focused therapies, mindfulness, and Compassion based therapies should also be further developed and tailored as therapeutic interventions (Braehler et al., 2013; McCarthy-Jones and Longden, 2015; Peters et al., 2016).

4.4. Limitations

There are several limitations of this study. First, the associations found are exploratory and non-causal as the temporal association was not determined. Second, childhood trauma may lead to differences in



Correlation of ACEs total score and Il6 expression in Schizophrenia and NCC group. *Significant at $p \leq 0.05$

Fig. 3. Adverse childhood events (ACEs total scores) and Il6 expression in Non-Clinical Control (NCC) and in the Schizophrenia group. Correlation of ACEs total score and Il6 expression in Schizophrenia and NCC group. *Significant at $p \leq 0.05$.

behavior as an adult, explaining differences in levels of peripheral immune markers. We attempted to control for this by excluding participants with known immune-modifying issues, including active addiction, and by examining for associations with antipsychotic medication normalized to CPZE. However, given that the clinical sample was comprised of only people with active, positive psychosis symptomology, yet reported current antipsychotic treatment, a third potential limitation is that the results may also only extend to persons who are more treatment resistant. Hence, for example, greater ACE scores in the patient sample may be a conclusion limited to generalize to persons who are more treatment refractory. A fourth limitation may be that the sample was also predominantly African American so conclusions may be limited to this group. Finally, we examined a small cohort of participants, using convenience sampling, and the findings may not be generalizable. We strongly encourage additional replication of this study in larger, more ethnically diverse cohorts.

4.5. Conclusion

In summary, this study shows a direct relationship between early childhood trauma, immunity and psychosis when examined along a continuum from non-clinical controls to psychotic disorders such as schizophrenia. The pathway from childhood trauma, to alterations in immunity, to symptoms of psychosis may represent a distinct psychiatric phenotype. The prevalence and severity of childhood trauma is characterized by both biological alterations and increased risk of experiencing symptoms of psychosis. Therefore, childhood trauma, through its effects on *IL6* levels, may be a risk factor for schizophrenia in general. This investigation provides novel results that contribute to the understanding of the intersect between childhood trauma, immunity and psychopathology.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.097.

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