Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Inflammation, substance use, psychopathology, and cognition in phase 1 of the clinical antipsychotic trials of intervention effectiveness study

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ARTICLE INFO

Article history:
Received 14 March 2017
Received in revised form 11 August 2017
Accepted 16 August 2017
Available online xxxx

Keywords:
Schizophrenia
Inflammation
Marijuana
Cocaine
Psychopathology
Cognition

ABSTRACT

Introduction: Schizophrenia has been associated with aberrant blood levels of inflammatory markers. However, patients with comorbid illicit drug use have been inadequately studied with respect to immune function. Furthermore, associations between inflammatory markers, psychopathology, and cognition have been inconsistently considered. We investigated relationships between inflammatory markers, comorbid marijuana and cocaine use, and psychopathology and cognition in patients with schizophrenia.
Method: For subjects with available fasting data from the baseline visit of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, inflammatory markers were investigated as predictors of psychopathology and cognition in patients with and without comorbid marijuana or cocaine use, using linear regression models controlling for potential confounding factors.
Results: Compared to subjects with a negative urine drug screen (UDS), marijuana use was a predictor of higher lymphocytes and E-selectin, and lower leptin ($p \leq 0.04$ for each); cocaine use was a predictor of higher adiponectin ($p = 0.04$). In subjects with marijuana use, lower WBC and higher IL-6 were predictors of higher PANSS total score ($p < 0.05$ for each). In subjects with cocaine use, lower total and differential WBC were predictors of higher PANSS total score ($p < 0.04$ for each). In younger, non-obese subjects with a negative UDS, higher monocytes and IL-6 were predictors of PANSS total score ($p < 0.04$ for each).
Conclusions: Our findings provide additional evidence that inflammation may be associated with psychopathology and cognition in some patients with schizophrenia. Furthermore, there is preliminary evidence for differential effects of comorbid marijuana and cocaine use on these relationships.
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1. Introduction

The investigation of immune system abnormalities in schizophrenia, though ongoing for decades, has more recently become a popular research area. This interest has been partially stimulated by our increased understanding of interactions between the immune system and the brain in other chronic medical disorders. Key replicated findings supporting the hypothesis that immune dysfunction may be involved in the pathophysiology of schizophrenia in some patients includes the following: 1) associations between genes involved in the regulation of the immune system and increased risk of schizophrenia (Psychiatric Genomics Consortium, 2014; Sekar et al., 2016; Shi et al., 2009); 2) prenatal maternal infection with a variety of different infectious agents is a risk factor for schizophrenia in the offspring (Brown and Derkits, 2010), and may act synergistically with family history of psychosis (Clarke et al., 2009); 3) there is a bidirectional association between psychosis and autoimmune disorders (Benros et al., 2014); 4) patients with schizophrenia have immune abnormalities in the blood, cerebrospinal fluid, and central nervous system, including immune cell numbers, inflammatory markers, and antibody titers (reviewed in Miller and Goldsmith, 2017); and 5) several trials have found that treatment with agents with anti-inflammatory properties may be associated with significant improvement in psychopathology in schizophrenia (Nitta et al., 2013; Sommer et al., 2014), and baseline blood levels of inflammatory markers may predict response to these agents (Laan et al., 2010; Muller et al., 2004). Taken together, these findings suggest we need to more systematically and extensively evaluate this hypothesis. Although some associations are well replicated, there is significant heterogeneity regarding findings for immune markers in schizophrenia, including negative studies. An important potential explanation for this observed heterogeneity is that immune system dysfunction occurs in only a subset of patients with schizophrenia, which may reflect an inherent limitation of our phenomenologically-based nosology. Another contributor to between-study heterogeneity is the inconsistent consideration of important potential confounding factors. Many previous studies of immune function in schizophrenia also did not explore

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http://dx.doi.org/10.1016/j.schres.2017.08.027
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Please cite this article as: Miller, B.J., et al., Inflammation, substance use, psychopathology, and cognition in phase 1 of the clinical antipsychotic trials of intervention effect..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.08.027

relationships between these markers and clinical features such as psychopathology and cognition. Several important populations of patients with schizophrenia have been inadequately studied with respect to immune function, most notably those with comorbid substance use. Illicit drug use has been an exclusion criterion in the majority of previous studies of the immunology of schizophrenia. Given the high prevalence of substance use comorbidity in patients with schizophrenia, and the potential for symptom exacerbation with illicit drug use, this represents an important potential selection bias. We may be excluding a subset of patients enriched with immune dysfunction who might also benefit—in terms of their psychotic disorder or substance use disorder or both, from anti-inflammatory or other immunotherapy treatment strategies.

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, we previously found associations between inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), leptin, and total and differential white blood cell (WBC) counts, and metabolic syndrome risk in patients with schizophrenia (Mori et al., 2015). Alterations in blood IL-6 levels are one of the most replicated inflammatory marker abnormalities in schizophrenia (Goldsmith et al., 2016). Several previous studies have found associations between IL-6 levels and psychopathology (Dimitrov et al., 2013; Chase et al., 2016; Frommberger et al., 1997; Pae et al., 2006) and cognition (Frydecka et al., 2015; Miller et al., 2013). In a meta-analysis, antipsychotic treatment of acute psychosis was also associated with significant decreases in blood IL-6 levels (Miller et al., 2011). Outside of schizophrenia, there is some evidence from a small number of studies that marijuana and cocaine use are also associated with alterations in blood IL-6 levels. Some studies have reported decreased blood IL-6 levels in lifetime marijuana users compared to controls (Keen and Turner, 2014; also reviewed in Suarez-Pinilla et al., 2014). Furthermore, one study found a significant interaction between lifetime marijuana use and higher blood IL-6 levels and worse cognitive function in African American adults (Keen et al., 2014). By contrast, one study found significantly higher blood IL-6 levels in women with cocaine use disorders compared to controls, and higher IL-6 levels were a predictor of greater cognitive impairments (Levandowski et al., 2016).

The purpose of this study is to investigate relationships between inflammatory markers, comorbid marijuana and cocaine use, and psychopathology and cognition in patients with schizophrenia. We hypothesize that compared to subjects with a negative urine drug screen, marijuana use will have lower and subjects with cocaine use will have higher blood IL-6 levels in patients with schizophrenia.

2. Material and methods

Data were obtained from the publicly available limited access CATIE schizophrenia trial dataset. A full description of the CATIE schizophrenia trial has been previously described (Lieberman et al., 2005). The study was deemed exempt by the Augusta University IRB. Blood for inflammatory markers, including total and differential WBC, CRP, IL-6, E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1), adiponectin and leptin were collected at baseline. A urine drug screen (UDS) was also obtained at baseline. Details on assay methodology for these inflammatory markers, have been described elsewhere (Meyer et al., 2009). Complete blood counts with differential were analyzed by standard clinical laboratory assays. Anthropometric measures, including height and weight, were also obtained at baseline. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Cognition was assessed using a battery of 11 tests that were reduced to 5 domains and a composite score; details on the CATIE neurocognitive battery has been described elsewhere (Keefe et al., 2006). Given the potential for diurnal variation and prandial effects on these blood markers, we only included subjects with fasting laboratory measures (last meal >8 h) in the analyses. We excluded subjects 1) currently taking scheduled non-steroidal anti-inflammatory, corticosteroids, or other immunomodulatory agents, 2) who reported taking antibiotics or other non-topical antimicrobial agents within 2 weeks of (either before or after) the baseline visit, and 3) subjects with current infectious diseases (e.g., hepatitis B or C, human immunodeficiency virus). Data on covariates, including age, sex, race, body mass index (BMI), smoking (number of cigarettes/day in the past week), and alcohol use (based on the Clinician Alcohol Use Scale) were also available. Subjects were stratified into three groups by baseline UDS: 1) negative UDS, 2) UDS positive for marijuana, and 3) UDS positive for cocaine. We excluded subjects with a UDS positive for both marijuana and cocaine, or for other substances such as amphetamines or opioids.

The data were analyzed using SPSS version 24 (SPSS, Inc.; Chicago, Illinois). Descriptive statistics (means, standard deviations, and proportions) were calculated for demographic and clinical variables. Variables that were significantly different between subject groups were included in the regression models. A one-sample Kolmogorov-Smirnov test was used to examine each variable for normality. All of the inflammatory markers, PANSS positive and negative subscale (but not PANSS total or general subscale) scores, and verbal memory, reasoning, and working memory (but not vigilance, processing speed, or cognitive composite scores) were not normally distributed, and were log transformed prior to the analyses.

We first compared levels of inflammatory markers between the three subject groups using the Kruskal-Wallis H-test, and post-hoc pair-wise comparisons using the Mann-Whitney *U* test. For any pairwise differences with a Mann-Whitney *U* test $p < 0.10$, we used linear regression models to evaluate subject group (negative UDS versus marijuana or cocaine use) as a predictor of inflammatory marker levels. Age, sex, race, smoking, BMI, and alcohol use were considered as potential confounding and/or moderating factors, and were included in the regression model if the variable 1) was significantly different between subject groups, or 2) was correlated with the inflammatory marker with a $p < 0.10$.

Next, within each of the three subject groups (considered separately), bivariate correlation coefficients (Spearman's rho) were calculated between inflammatory markers, psychopathology, and cognition. We further investigated any correlations between inflammatory markers and psychopathology or cognition with a $p < 0.10$ using linear regression models. Age, sex, race, smoking, BMI, and alcohol use were considered as potential confounding and/or moderating factors, and were included in the regression model if the variable was correlated with the psychopathology or cognitive measure with a $p < 0.10$. In the analysis of subjects with a negative UDS, 1) younger age (<40) and lower BMI (<30) were predictors of higher levels of psychopathology, and 2) older age (>40) and abstinence from alcohol were predictors of greater cognitive impairment. Therefore, in post-hoc analyses we investigated the relationship between inflammatory markers, psychopathology, and cognition in these subgroups as detailed above. For all analyses, results were considered statistically significant at the $\alpha = 0.05$ level (two-sided). Given the exploratory nature of the analyses, we did not correct for multiple comparisons, although we used the correlative data to reduce the number of linear regression models investigated.

3. Results

Table 1 presents the demographic and clinical characteristics of the study sample. The total sample consisted of $n = 556$ subjects, including $n = 490$ with a negative UDS, 47 with a UDS positive for marijuana, and 19 with a UDS positive for cocaine. The number of subjects with available data on inflammatory markers ranged from 475 (for adiponectin) to 555 (for ICAM-1 and VCAM). PANSS data were available for 551 subjects, and data on cognition was available for 516 subjects. Data were available for at least 97% of subjects for all other covariates.

Age, race, alcohol use, IL-6, and leptin levels were significantly different across the three subject groups ($p < 0.03$ for each). In post-hoc pairwise comparisons, for subjects with a UDS positive for marijuana

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