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Short communication

Infection and inflammation in schizophrenia and bipolar disorder

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ABSTRACT

The present study investigated the relationship between exposure to infectious agents and inflammation markers in individuals with schizophrenia (SZ), bipolar disorder (BP), and controls without a psychiatric disorder. We measured plasma levels of antibodies and innate immune markers and correlated them with clinical symptoms and cognitive function. In both SZ and BP, we found an increase in soluble CD14, and in BP an increase in C-reactive protein, IgM class antibodies against cytomegalovirus (CMV), and IgG class antibodies against herpes simplex virus 2. Furthermore in BP, we observed a negative relationship between IgG antibodies against CMV and scores for cognitive function.

Involvement of infection and inflammation was suggested in the pathology of major mental illness (Horváth and Mirnics, 2014; Watkins et al., 2014; Landek-Salgado et al., 2016; Owen et al., 2016). Many studies investigated this question in schizophrenia (SZ) but fewer studies evaluated bipolar disorder (BP) (Brietzke et al., 2009; Munkholm et al., 2013; Hayes et al., 2014; Coughlin et al., 2016). In SZ, several studies reported increased antibody levels against Toxoplasma gondii (T. gondii) and cytomegalovirus (CMV) (Leweke et al., 2004; Sutterland et al., 2015). However, fewer studies measured antibody levels in BP patients, and some studies failed to replicate the observations (Tedla et al., 2011; Hamdani et al., 2013; Dickerson et al., 2015; Prossin et al., 2015; Stich et al., 2015; Sutterland et al., 2015). We previously reported that changes in neuroinflammatory mediators, such as reduction of interleukin-6 receptor (IL-6R) and angiotensin converting enzyme (ACE), were correlated with the levels of antibodies against T. gondii and herpes simplex virus-1 (HSV-1) in the cerebrospinal fluid from subjects with psychosis, suggesting a link between infection and alterations in immune inflammatory cascades (Hayes et al., 2014). It is important to solidify the basic idea that infection and inflammation are involved in the pathology of major mental illness by testing further cohorts.

Accumulating evidence in neurobiology indicated that activation and alteration of immune inflammatory cascades directly affect neural connectivity and circuitry (Fourgeaud and Boulanger, 2010; Landek-Salgado et al., 2016). For example, tumor necrosis factor alpha (TNFα) derived from glia were shown to modulate neural excitability by decreasing AMPA receptors on inhibitory striatal medium spiny neurons, but increasing AMPA receptors on excitatory hippocampal neurons (Beattie et al., 2002; Stellwagen and Malenka, 2006; Lewitus et al., 2014). These changes in excitability induced by a neuroinflammatory mediator demonstrate that alteration of immune cascades can impact brain function through region and cell specific mechanisms. Furthermore, recent studies into infection and inflammation in mental illness examined the relationship between neuropsychological measures and clinical demographics with underlying changes in immune mediators (Prasad et al., 2012). Specifically, studies showed that increased serological levels of CMV, HSV-1, T. gondii, and C-reactive protein (CRP), an inflammation marker, were correlated with worse neurocognitive performance in SZ and/or BP (Dickerson et al., 2004, 2013, 2014; Shirts et al., 2008). Nonetheless additional cohorts for both SZ and BP are needed.

To address these needs, the present study evaluated SZ and BP in comparison with healthy controls. We measured the

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Table 1
Clinical and demographic characteristics and values for inflammatory markers in SZ patients and matched controls (Con). Paired *t*-test was used for age, years of education, antibody levels, and inflammatory markers. McNemar significance probability was used for gender and ethnicity, and Cochran's Q test was used for smoking status. One participant refused PANSS and BACS assessment. Significant values are indicated in bold ($p < 0.05$).

Characteristics	Con (N = 28)	SZ (N = 28)	p value
Age	37.86 ± 9.24	39.00 ± 8.83	**0.029**
Gender (Male/Female)	18/10	18/10	1.000
Ethnicity (AA/C/Indian)	22/6/0	22/6/0	1.000
Smoking (Non/Current/Unknown)	17/11/0	8/20/0	0.064
Years of Education (16 Con-SZ pairs)	12.00 ± 2.13	12.75 ± 2.21	0.409
Chlorpromazine equivalents (mg, 13 patients)	–	378.80 ± 281.63	–
Antipsychotics (yes/no)	–	21/7	–
Antidepressant (yes/no)	–	5/23	–
Mood Stabilizers (yes/no)	–	7/21	–
Minor Tranquilizers (yes/no)	–	3/25	–
PANSS Total	–	63.26 ± 17.36	–
BACS Average	–	31.62 ± 7.36	–
CMV IgG	4.545 ± 2.392	3.997 ± 2.054	0.338
CMV IgM	0.068 ± 0.098	0.065 ± 0.039	0.860
T. gondii IgG	0.689 ± 0.783	0.693 ± 0.222	0.982
T. gondii IgM	0.146 ± 0.141	0.155 ± 0.129	0.771
HSV-1 IgG	1.999 ± 1.204	2.252 ± 1.293	0.472
HSV-2 IgG	1.336 ± 1.230	1.420 ± 1.433	0.791
CRP	2819.97 ± 2829.04	4143.52 ± 3383.92	0.156
Pentraxin-3	0.793 ± 1.324	0.310 ± 0.188	0.067
Soluble CD14	3527.26 ± 1927.36	4481.09 ± 916.88	**0.038**

antibody levels of infectious agents (T. gondii, CMV, HSV-1 and HSV-2) and three inflammatory markers [CRP, pentraxin-3, and soluble CD14 (sCD14) a secreted receptor in response to infections]. Next, we assessed the possible correlation of these plasma measures with neurocognitive functions or symptom severity in SZ and BP. The Institutional Review Board of the Johns Hopkins University approved the study, and written informed consent was obtained from all subjects after a description of the study.

The SZ group consisted of 28 patients with DSM-IV clinical diagnoses of SZ and schizoaffective disorder, and the BP group included 32 patients with bipolar disorder type I or II. Both the SZ and BP groups were newly enrolled at outpatient community psychiatry clinics/programs at Johns Hopkins Hospitals. Patients were recruited between August 1, 2008 and December 2014 using flyers and staff referrals. None of the individuals were in their first lifetime episode of illness and the duration of illness varied. Sixty healthy comparison subjects who did not meet the DSM-IV criteria for an axis I psychiatric disorder were pair-matched from other studies [Baltimore Epidemiologic Catchment Area (ECA) follow up study (Eaton et al., 2007), Prevention Research Center (PRC) intervention trial (Storr et al., 2014), and Johns Hopkins Schizophrenia Center (Toritsuka et al., 2013)]. All patients completed a structured interview for diagnostic assessment. Twenty-seven SZ patients completed the Positive and Negative Syndrome Scale (PANSS) and the Brief Assessment of Cognition in Schizophrenia (BACS); 32 BP patients completed the BACS, and 31 BP patients completed the PANSS (Kay et al., 1987; Keefe et al., 2004).

Controls were pair-matched with the patient groups for age, gender, and ethnicity, but the SZ patients were significantly older by ~1 year ($p = 0.029$) (Table 1). BP and healthy controls were well matched on age, gender, ethnicity, smoking status, and years of education (Table 2). Statistical analyses were performed using STATA 13.1 for Macintosh (College Station, Texas, USA). Both the SZ and BP groups self-reported medication usage because the participants were new enrollments to the present study. Group comparisons of demographic and clinical data were calculated using paired *t*-tests, McNemar test, or Cochran's Q test. Statistical significance was defined as $p < 0.05$. For the PANSS scores we used a regression analysis and adjusted for the three subscale scores (positive, negative, and general psychopathology), and significance was set at $p < 0.05/3$ (=0.0167).

To address the exposure to infectious agents, we used enzyme immunoassays for IgG class antibodies to CMV, HSV-1, HSV-2, and T. gondii, as well as those for IgM class antibodies to T. gondii and CMV (Leweke et al., 2004; Avramopoulos et al., 2015). The levels of Pentraxin-3, CRP, and sCD14 were measured by solid phase immunoassay (Severance et al., 2013; Dickerson et al., 2015). We did not observe any significant differences in the six antibody levels between SZ and controls (Table 1). In BP, we observed a significant increase in the levels for CMV IgM ($p = 0.012$) and HSV-2 IgG ($p = 0.023$) compared to healthy controls using linear regression (Table 2). We confirmed these findings using McNemar test of HSV-2 IgG seropositive (>1.0) compared to seronegative (≤1.0) and found consistent results ($p = 0.092$, CMV IgM titer levels did not have seropositivity cutoff values). Among the three inflammatory markers, SZ patients showed a significant increase only in sCD14 ($p = 0.038$) compared with controls (Table 1). However, BP patients showed a significant increase in both CRP ($p = < 0.001$) and sCD14 ($p < 0.001$) compared to controls (Table 2). Statistical comparisons of the six antibody levels and three inflammation markers were performed with a both a paired *t*-test and regression analysis using age and smoking status as covariates.

Symptoms were assessed using the PANSS (Kay et al., 1987), and cognitive function was assessed using the BACS (Keefe et al., 2004). The composite BACS score, as an indicator of overall neurocognitive function, was calculated by averaging the scores of six sub-domains (working memory, motor speed, verbal fluency, attention, speed of information processing, and executive function). In SZ, there was no significant relationship between the PANSS/BACS scores and the antibody levels or inflammation markers (Table 3). In BP, there was a significant negative relationship between CMV IgG and BACS average score ($p = 0.019$) that remained significant