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Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls

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ABSTRACT

Background: The mechanisms underlying cognitive impairment in schizophrenia and bipolar disorders are largely unknown. Immune abnormalities have been found in both disorders, and inflammatory mediators may play roles in cognitive function. We investigated if inflammatory markers are associated with general cognitive abilities.
Methods: Participants with schizophrenia spectrum (N = 121) and bipolar spectrum (N = 111) disorders and healthy controls (N = 241) were included. General intellectual abilities were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI). Serum concentrations of the following immune markers were measured: Soluble tumor necrosis factor receptor 1 (sTNF-R1), interleukin 1 receptor antagonist (IL-1Ra), osteoprotegerin, von Willebrand factor, C-reactive protein, interleukin-6 and CD40 ligand.
Results: After adjusting for age, sex and diagnostic group, significant negative associations with general cognitive function were found for sTNF-R1 ($p = 2 \times 10^{-5}$), IL-1Ra ($p = 0.002$) and sCD40 ligand ($p = 0.003$). Among patients, the associations remained significant ($p = 0.006$, $p = 0.005$ and $p = 0.02$) after adjusting for possible confounders including education, smoking, psychotic and affective symptoms, body mass index, cortisol, medication and time of blood sampling. Subgroup analysis, showed that general cognitive abilities were significantly associated with IL-1Ra and sTNF-R1 in schizophrenia patients, with sCD40L and IL-1Ra in bipolar disorder patients and with sTNF-R1 in healthy controls.
Conclusion: The study shows significant negative associations between inflammatory markers and general cognitive abilities after adjusting for possible confounders. The findings strongly support a role for inflammation in the neurophysiology of cognitive impairment.

1. Introduction

Schizophrenia spectrum disorder (SCZ) and bipolar spectrum disorder (BD) affect 2% of the population and cause marked decrements in quality of life and life expectancy (Whiteford et al., 2013). The core characteristic of SCZ is psychotic symptoms, while affective symptoms are at the core of BD. There is however, an overlap in these symptoms, as described in continuum hypotheses of the two disorders (Craddock and Owen, 2010). It has been increasingly recognized that cognitive deficits are among the core symptoms in both disorders, persistent across acute and chronic phases and associated with reduced functional outcome (Simonsen et al., 2010, 2011; Bourne et al., 2013). Recently, the NIMH Research Criteria Project suggested that cognition should be one of five core research domains in the field of psychiatric diseases (Morris and Cuthbert, 2012).

SCZ and BD are highly heritable disorders (Lichtenstein et al., 2009) with complex genetic and environmental interactions involved (Burmeister et al., 2008). Several lines of research indicate that the immune system may be involved in these interactions (Kinney et al., 2010) and it has been suggested that mononuclear phagocyte cells including microglial cells may play a key role in their pathogenesis.

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Increased macrophage/monocyte inflammatory activation and enhanced immune gene expression in circulating monocytes have been described in both BD and SCZ (Beumer et al., 2012; Bergink et al., 2014). Altered cytokine levels with elevated activity in the immunological signal pathways of tumor necrosis factor (TNF), and interleukin (IL)-1, IL-2, IL-4 and IL-6 have also been found in both disorders (Potvin et al., 2008; Drexhage et al., 2010; Munkholm et al., 2013). These elevations are of importance as animal studies suggest that elevated inflammatory signals may directly influence neuronal synaptic dynamics and neurotransmission and have a negative impact on cognitive abilities (Boulanger, 2009; Shatz, 2009; Havik et al., 2011). Levels of inflammatory markers are determined by both genetic and environmental factors (Neijts et al., 2013), and could be regarded as partly trait and state characteristics. Stress hormones such as cortisol and changes in the hypothalamic–pituitary–adrenal axis may have a marked effect on both inflammation and cognition (Himmerich et al., 2006; Kinney et al., 2010).

We have previously measured the activity in three cytokine pathways described to play major roles in a cytokine model of cognition (McAfoose, 2009): the IL-1 receptor antagonist (IL-1Ra), soluble TNF receptor 1 (sTNF-R1) and IL-6 as markers of TNF, IL-1 and IL-6 activity. In addition we measured the activity in von Willebrand factor (vWf) as a marker of endothelial cell activation, osteoprotegerin (OPG) as a marker of calcium related vascular inflammation, soluble CD40 ligand as platelet activation (sCD40L), and C-reactive protein (CRP) as a reliable down-stream marker of inflammation mainly produced in the liver. We found elevated levels of inflammatory markers in SCZ and BD (Hope et al., 2009, 2010). Subsequent studies showed that higher levels of proinflammatory cytokines were associated with increased psychotic symptoms (Hope et al., 2011b, 2013), affective state and degree of affective symptoms in BD (Hope et al., 2011a), and brain morphology (Dieset et al., 2014).

Enhanced immune activation, as measured by markers of inflammation has been found to correlate with poorer cognitive function in patients with neurological diseases and in healthy persons (Cunningham et al., 2009b; Patanella et al., 2010; Balldin et al., 2012; Bettcher and Kramer, 2014; Rocha et al., 2014). In SCZ, a systematic literature review investigating the relationship between cognition and inflammation found evidence of a negative association between high sensitivity CRP and cognition (Ribeiro-Santos et al., 2014), and in addition, a recent study showed a positive correlation between IL-2 and non-verbal intelligence (Asevedo et al., 2014). However, all studies measured activity in a single proinflammatory marker and none controlled for possible confounders e.g. smoking, body mass index, medication, or clinical severity measures. In BD, a recent meta-analysis found two studies that had found an association between a central inflammatory marker and cognition (Bauer et al., 2014) and in addition, a recent study in older patients found an association between inflammation and cognitive function (Lotrich et al., 2013). However, none of the studies measured activity in more than one of the central inflammatory pathways, nor did they control for possible confounding factors such as autoimmune disease, education or clinical severity measures. As several studies have reported that affective symptoms are associated with inflammatory markers (Hope et al., 2011b), affective states should be included as possible covariates. Thus, in both BD and SCZ, there are a lack of studies investigating how markers of different inflammatory pathways relate to general cognition after adjusting for both clinical severity measures and somatic characteristics.

A person's general cognitive abilities are relatively stable up to 60 years of age (Hedden and Gabrieli, 2004), and may be measured through general intelligence quotient (IQ) tests (Gottfredson, 1998). The Wechsler Abbreviated Scale of Intelligence (WASI) is a neuropsychological test battery that estimates a full scale IQ (FSIQ) that correlates highly with IQ estimates obtained through the Wechsler Adult Intelligence Scale (WAIS-III) FSIQ (Ryan et al., 2003; Bosnes, 2009). The WASI also estimates performance IQ (fluid intelligence) and verbal IQ (crystallized intelligence), and has been validated across psychiatric patient groups (Hays et al., 2002). Based on the proposed role of inflammatory markers in the pathophysiology of severe mental illness, we hypothesized that increased levels would be related to reduced general cognitive abilities as measured with the WASI. The role of immune-related factors has been better documented in SCZ than in BD (Altamura et al., 2014; Andreassen et al., 2014) and possibly stronger associations may be present in SCZ than in BD. This has not been investigated before. Furthermore, inflammatory mediators may reflect physiological processes also in the absence of a severe mental illness (Boulanger, 2009; Shatz, 2009; Havik et al., 2011), and we wanted to investigate if associations between inflammatory markers and cognition could be found also in healthy volunteers.

The aim of the current study was to determine how markers of different proinflammatory pathways (sTNF-R1, IL-6, IL-1Ra, OPG, vWf, sCD40L and hsCRP) relate to general cognitive abilities in large well-characterized samples of SCZ and BD patients and healthy controls after adjusting for disease severity measures and somatic characteristics and other possible confounding factors.

2. Methods

2.1. Participants

The current sample has been described in previous publications (Hope et al., 2009, 2013; Simonsen et al., 2011). Briefly, patients from the catchment area of Oslo University Hospital and collaborating hospitals to the ongoing Thematically Organized Psychosis (TOP) Study in Oslo, Norway were included. Most patients received outpatient treatment. Inclusion criteria were as follows: Caucasian patients registered in the psychiatric services of Oslo University Hospital and collaborating hospitals; 18 to 63 years of age; and meeting DSM-IV criteria for SCZ or BD. Exclusion criteria were as follows: First language other than Norwegian, organic psychosis, neurological disorder, head injury with electroencephalogram (EEG)-, computer tomography (CT)- or magnetic resonance imaging (MRI)-scanned abnormalities following the injury, intellectual disability, autoimmune disease or use of non-steroid anti-inflammatory drugs (NSAIDs). The participants were included between 2003 and 2008. Included in the current analyses were 226 consecutively referred patients of whom 121 patients had a schizophrenia spectrum disorder (SCZ) (schizophrenia [93], schizophreniform [N = 8] and schizoaffective disorder [N = 20]), and 111 patients had a bipolar spectrum disorder (BD) (bipolar I disorder [N = 65], bipolar II disorder [N = 40] and BD not otherwise specified [N = 6]).

Healthy controls from the same catchment area as the patients (Oslo and suburbs) were randomly selected from statistical records (www.ssb.no) and invited by letter. Included in the study were 241 persons without a history of medical diseases, severe psychiatric disorders, including alcohol or illicit substance abuse, or SCZ or BD in first-degree relatives.

Both patients and healthy controls were assessed by trained psychiatrists or clinical psychologists. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes. Inter-rater reliability was good, with an overall kappa score of 0.77 (95% confidence interval: 0.60–0.94) for diagnoses (Ringen et al., 2008).

Clinical characteristics were assessed with the Positive and Negative Syndrome Scale (PANSS), General Assessment of Functioning (GAF), Young Mania Rating Scale (YMRS), and Inventory of Depressive Symptomatology (IDS)/Calgary Depression Scale for Schizophrenia (CDSS). Affective state was based on scores on YMRS and IDS/CDSS, as described previously (Hope et al., 2011b). For all participants, daily smoking, number of alcohol units and episodes of substance abuse during the last 2 weeks prior to assessment were recorded, as well as level of education, duration of illness and scores on the National Adult Reading Test (NART) (Russell et al., 2000). All participants gave written informed