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Impaired functioning in euthymic patients with bipolar disorder — HSV-1 as a predictor ☆

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ABSTRACT

There is a possible association between infectious agents and psychiatric disorders. Previous studies in the US provided evidence for cognitive impairment correlated with Herpes simplex virus type 1 (HSV-1) infection. For a replication study in Europe we chosed individuals diagnosed with bipolar disorder to analyse the correlation with HSV-1 infection. Antibody prevalence was analyzed by using solid phase immunoassay techniques. Cognitive functioning was tested with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Form A, the Trail Making Test A&B, and two subtests from the WAIS III: the Letter Number Sequencing Task and the subtest on information. History and psychopathology was assessed using structured interviews and validated rating scales (SCID, HRSD-21, YMRS, PANSS). Additionally, we investigated social functioning and quality of life using self-assessment-scales (SAS, LQLP). Prevalence rates of antibodies against diverse infectious agents did not differ significantly between patients and controls. We found a significant correlation between cognitive impairment in patients with bipolar disorder and the prevalence of antibodies directed against HSV-1. Cognitive functions were significantly impaired including language, attention, and immediate memory.
The results of this study confirm previous findings suggesting that HSV-1 affects cognitive functions in patients with bipolar disorder. This may also result in more impaired functioning, less quality of life and difficulties in social adjustment.

1. Introduction

Bipolar disorder is the sixth-leading cause of disability worldwide and presents a significant burden for affected individuals and their families with serious socioeconomic consequences (Dean et al, 2004; Merikangas et al, 2007). The underlying pathophysiological mechanisms of bipolar disorder are not yet fully understood and may be manifold. Impaired function displayed as activation abnormalities of the dorsolateral prefrontal cortex and of the anterior cingulum were found with functional magnetic resonance imaging (fMRI) in euthymic bipolar patients (McDonald et al, 2004). Decreased glial and neuronal density in prefrontal cortex areas as well as disturbances of the various neurotransmitter systems may be implicated in the pathogenesis of bipolar disorder (Rajkowska et al, 2001; Sobczak et al, 2002). But there is also preliminary evidence for a role of infectious agents in bipolar disorder. Dickerson and coworkers (Dickerson et al., 2003, 2004, 2006) found an association between herpes simplex virus type 1 (HSV-1) and cognitive impairment in bipolar disorder and schizophrenia. The objectives of the present study were to replicate and extend these findings by examining correlates of infection, cognitive functioning, and demographic parameters and relate these parameters to the prevalence of antibodies to infectious agents in patients with bipolar disorder. Additionally; we collected data

Abbreviations: HSV, Herpes simplex virus; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WAIS III, Wechsler Adult Intelligence Scale III; HAWIE-R, Hamburg-Wechsler-Intelligenztest für Erwachsene; SCID, Structured Clinical Interview Diagnostic for DSM-IV; HRSD-21, Hamilton Rating Scale for Depression 21; YMRS, Young Mania Rating Scale; PANSS, Positive and Negative Syndrome Scale; SAS, Social adjustment scale; LQLP, Lancashire quality of life profile; fMRI, functional magnetic resonance imaging; DNA, deoxyribonucleid acid; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpes virus; VZV, varicella zoster virus; IgG, immunoglobulin G; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; TMT A&B, Trail Making Test A&B; LNST, Letter-Number Sequencing Task; gG1, gG2, glycoproteins; ANOVA, analyses of variance.

☆ This study was conducted at the Dept. of Psychiatry, University of Freiburg, Germany and at the Stanley Neurovirology Laboratory, Johns Hopkins University Medical Center, Baltimore, MD.

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about quality of life and social functioning of patients and controls in order to determine the extent of psychosocial consequences in HSV-1 seropositive individuals with bipolar disorder

Infectious microorganisms such as herpes simplex virus (HSV), and *treponema pallidum* have been shown to be involved in the pathogenesis of neurological and psychiatric disorders (Ledgerwood et al, 2003; Strandberg et al, 2005; Yolken, 2004). *Herpesviridae* are enveloped double-stranded DNA viruses causing lifelong infection and possible recurrent reactivation (Steiner et al, 1994). They include HSV-1, HSV-2, cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpes virus 6 (HHV-6), and varicella zoster virus (VZV). Cerebral CMV infection can cause cellular damage by apoptosis and glial cell activation (Lokensgard et al, 2002), processes reportedly involved in schizophrenia (Cotter et al, 2001).

An increased presence of immunoglobulin G (IgG) antibodies to the protozoon *Toxoplasma gondii* has been found in recent-onset schizophrenia and was linked to impaired cognitive functioning (Ledgerwood et al, 2003; Leweke et al, 2004).

Cognitive dysfunction in bipolar disorder has been described for sustained attention (Clark et al, 2002), information processing speed (Tham et al, 1997), figural, declarative, and working memory (Ferrier et al, 1999; Rubinsztein et al, 2000), global cognitive function (Kessing, 1998), and problem-solving strategies (Scott et al, 2000). Continued neuropsychological impairment has been shown to persist for a period as long as three years and possibly longer (Balanza-Martinez et al, 2005). The findings of a comparative study of neurocognitive function in euthymic bipolar patients and stabilized schizophrenic patients support the notion that euthymic bipolar patients suffer from an extensive neurocognitive impairment that affects all cognitive domains. In addition these findings suggest clinical relevance of persistent verbal memory impairment in bipolar patients because they correlate with poor psychosocial function (Sanchez-Morla et al, 2009).

Taking these findings into account we investigated social functioning and quality of life as meaningful consequences of selective or overall functional impairment, possibly related to the presence of infectious agents (Figueira and Ouakinin, 2008). A link between mental health and the immune system has been well established, andrecent studies described interactions of immune dysregulation and mental stress (Figueira and Ouakinin, 2008).

Social functioning and quality of life are the most relevant outcomes for patients and relatives. A recent extensive review on functioning and disability in bipolar disorder has shown that bipolar disorder is associated with significant impairment in work, family and social life, not only during acute phases of the illness, but also after recovery. Subsyndromal symptoms and neurocognitive impairment increase the risk of low functioning and disability in bipolar patients.(Sanchez-Moreno et al, 2009).

The presence of HSV-1 antibodies has been shown as an independent predictor of decreased cognitive functioning with a US sample with bipolar disorder (Dickerson et al, 2004). It is also known that acute exacerbation of the infection in virus carriers may be associated with an elevated stress level and its immunosuppressive effect (Glaser et al, 1987). That could lead to a vicious circle with psychosocial stress resulting in a new manic or depressed episode, exacerbated HSV-1 infection, and, as a result, increasing functional impairment and poor quality of life.

However, the level of psychosocial stress and, by this, incidence of both mental disorders and apparent HSV-1 infections may vary between cultures and populations. In addition, environmental and behavioural factors might modulate both infestation rate and virulence of infectious diseases. Therefore, we felt that it was important to verify the findings of the US based study in a different sample, and also have a closer view on the consequences for everyday life of patients with more severe cognitive impairment.

2. Methods

2.1. Patient population and study design

The present study was done to investigate and replicate the association between neurocognitive deficits and HSV-1 seropositive European individuals with a previously diagnosed bipolar disorder according to DSM IV-criteria. The study design refers to a previous US based study, which showed a correlation between the two variables (Dickerson et al, 2006). Subjects had to fullfil the following inclusion criteria:

Outpatients between 18 and 65 years with a diagnosis of bipolar disorder according to DSM IV, being euthymic for at least for 1 month with a score <7 on the Hamilton Rating Scale for Depression (HRSD-21) and the Young Mania Rating Scale (YMRS), respectively. Furthermore, subjects should not suffer from mental retardation or learning disabilities, substance abuse, clinically significant medical condition that could affect cognitive outcome, acute herpes simplex infection, and should not take any antiviral medication. Following these criteria, we included 30 patients with bipolar disorder from our outpatients clinic and 20 unaffected controls. Because of the small numbers, we did not further divide the sample into bipolar I and II. Controls had to fulfil same inclusion criteria and, in addition, had to be without a history of mental disorder, psychiatric or psychological treatment and were matched for gender, education and age. Patients and controls had to give written informed consent. This study was approved by the ethics committee of the University of Freiburg, Germany.

2.2. Assessment instruments

2.2.1. Clinical diagnostic and psychometric scales

The diagnosis of bipolar disorder was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Patients and controls underwent the Structured Clinical Interview Diagnostic for DSM-IV (SCID) (First et al, 1996; Wittchen et al, 1997).

To verify euthymia and detect possible psychotic symptoms, all participants were assessed with the Hamilton Rating Scale for Depression (HRSD-21), the Young Mania Rating Scale (YMRS), and the Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987) at the time of neurocognitive testing. Neuropsychological function was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status, Form A (RBANS) (Randolph et al, 1998) and by the Trail Making Test (TMT A&B), which tests processing speed and cognitive flexibility (Bowie and Harvey, 2006). Additionally, two subtests from the Wechsler Adult Intelligence Scale (WAIS III, German version HAWIE-R) (Tewes, 1991; Wechsler, 1997) were included: the Letter-Number Sequencing Task (LNST) which was used as an independent measure of working memory, and the subtest on general information.

The RBANS consists of 12 subtests giving a total score, and five index scores for the tested domains of cognitive functioning: immediate memory (list learning, story memory), visuospatial/constructional abilities (figure copy, line orientation), language (picture naming, semantic fluency), attention (digit span, coding), and delayed memory (list recall, story recall, figure recall, list recognition). Each raw value was transformed into an age-adjusted standard score with an average of 100 and a standard deviation of 15, based on a normative study group of 540 healthy subjects.

2.2.2. Serological analysis

Analyses were done at the Stanley Laboratory of Developmental Neurovirology, John Hopkins University School of Medicine, Baltimore, MD, USA. Solid phase immunoassay techniques were used to quantify IgG class antibodies to human herpes viruses in the sera of patients with bipolar disorder and healthy controls. Binding specificity is a key feature of immunoassays. Immunoassays are based on the ability of an