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Perceived stress and hair cortisol: Differences in bipolar disorder and schizophrenia

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ABSTRACT

Introduction: Bipolar disorder (BD) and schizophrenia (SCZ) are psychiatric disorders with shared and distinct clinical and genetic features. In both disorders, stress increases the risk for onset or relapse and dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis has been reported. The latter is frequently investigated by measuring changes in the hormonal end product of the HPA axis, i.e., the glucocorticoid cortisol, whose concentration exhibits diurnal variation. The analysis of hair cortisol concentration (HCC) is a new method, which allows assessment of cumulative cortisol secretion over the preceding three months.

Aims: To explore whether perceived stress and HCC: (i) differ between BD patients, SCZ patients, and controls; (ii) change over disease course; and iii) are associated with an increased genetic risk for BD or SCZ.

Methods: 159 SCZ patients, 61 BD patients and 82 controls were included. Assessment included psychopathology, perceived stress, and HCC. Inpatients with an acute episode (38 BD and 77 SCZ) were assessed shortly after admission to hospital and at 3 and 6 months follow-up. Outpatients in remission and controls were assessed at one time point only. Polygenic risk scores for BD and SCZ were calculated based on results of the Psychiatric Genomic Consortium.

Results: (i) Perceived stress was higher in BD and SCZ patients compared to controls ($p < 0.02$), and was lower in outpatients in remission compared to inpatients on admission. HCC was higher in BD patients compared to SCZ patients and controls ($p < 0.02$), and higher in inpatients on admission than in outpatients in remission ($p = 0.0012$). In BD patients ($r = 0.29$; $p = 0.033$) and SCZ patients ($r = 0.20$; $p = 0.024$) manic symptoms were correlated with HCC. (ii) In both BD and SCZ inpatients, perceived stress decreased over the 6 month study period ($p = 0.048$), while HCC did not change significantly over the 6 month study period. (iii) In controls, but not in the patient groups, the genetic risk score for BD was associated with HCC ($r = 0.28$, $p = 0.023$).

Conclusions: While our results are consistent with previous reports of increased perceived stress in BD and SCZ, they suggest differential involvement of the HPA axis in the two disorders. The genetic study supports this latter finding, and suggests that this effect is present below the threshold of manifest disorder.

Abbreviations: BD, bipolar disorder; SCZ, schizophrenia; HPA axis, hypothalamus-pituitary-adrenal axis; HCC, hair cortisol concentration.

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1. Introduction

Bipolar disorder (BD) and schizophrenia (SCZ) are heterogeneous psychiatric disorders with distinct as well as overlapping clinical features. Extensive research evidence implicates stress in the etiology of both illnesses. Patients report higher stress levels (psychosocial, chronic stress) than healthy controls (Pruessner et al., 2011). Furthermore, stressful life events increase risk for both SCZ (Tessner et al., 2011), and BD (Hillegers et al., 2004; Horesh et al., 2011), and trigger relapse in SCZ (Chabungbam et al., 2007; Fallon, 2009) and BD patients (Altman et al., 2006).

A core element of the biological stress response is the hypothalamus-pituitary-adrenal (HPA) axis, whose activation leads to the secretion of the hormone cortisol (Chrousos, 2009). Increasing evidence suggests that the association between stress and psychotic disorders is mediated via altered regulation of the HPA axis (Daban et al., 2005; Holtzman et al., 2013). Research has shown that stressful life events and chronic stress dysregulate cortisol levels, thereby increasing stress vulnerability and the risk for disease onset or relapse (Corcoran et al., 2001; Miller et al., 2007; van Winkel et al., 2008). In SCZ and BD patients, research has demonstrated altered cortisol levels (Bradley and Dinan, 2010; Havermans et al., 2011). For both disorders, increased basal cortisol secretion has been reported (Steen et al., 2014, 2011). This has been attributed to reduced glucocorticoid receptor mediated negative feedback of the HPA axis (Daban et al., 2005). Additionally, blunted reactivity to stress has been reported in both BD (e.g. Houtepen et al., 2015; Wieck et al., 2013), and SCZ (review see Ciufolini et al., 2014). Interestingly, elevated cortisol levels have also been reported in individuals at increased risk for psychosis, in particular those who subsequently develop psychosis (Cullen et al., 2014; Walker et al., 2013). Studies have also demonstrated altered HPA axis regulation and increased cortisol levels in relatives of psychotic patients (Collip et al., 2011; Yildirim et al., 2011) and the healthy offspring of BD patients, i.e., individuals with a higher genetic risk for the disorder (Ellenbogen et al., 2010; Ostiguy et al., 2011). However, these data do not elucidate the relationship between altered HPA axis activity and increased risk, i.e., whether increased cortisol is the consequence or the trigger for symptom exacerbation (see discussion in Walker et al., 2013). Furthermore, it remains unclear whether HPA axis activity differs between subgroups of patients, and whether the time point at which cortisol is measured during the course of the disorders influences cortisol levels. Irrespective of these considerations, cortisol may be a useful biomarker in the investigation of the biological mechanisms that underlie etiology and propensity to relapse in BD and SCZ.

In this context, an important new development is the assessment of hair cortisol concentrations (HCC) in humans. This method provides a retrospective measure of cumulative cortisol secretion over prolonged time-periods, and this measure is robust against variation caused by reactions to transient stressors or diurnal fluctuation. Typically, a 3 cm segment of scalp hair is assessed to determine cortisol secretion during the preceding three months (see Gow et al., 2010 for a review).

Increased HCC has been demonstrated in individuals exposed to prolonged stress. For example, increased HCC has been found in subjects with a history of trauma (Steudte et al., 2011a), and altered HCC has also been found in generalized anxiety disorder and individuals who are unemployed (Dettenborn et al., 2010; Steudte et al., 2011b). A recent study of HCC and BD comprising 100 BD patients and 195 controls found increased HCC in the subgroup of BD patients with an age at onset of >30 years (Manenschijn et al., 2012). In a subsequent study, the authors found that recent negative life events were associated with increased HCC in patients with BD (Staufenbiel et al., 2014).

Table 1
Demographic characteristics: Age and sex distribution in patients with bipolar disorder (BD) and schizophrenia (SCZ), and in controls. M = males, F = females.

	SCZ	BD	Controls	p
Age	40,29 (11.46)	45.12 (10.61)	32.92 (12.40)	<0.01
M:F ratio	58:101	19:42	33:49	0.53
N total	159	61	82	

Studies measuring cortisol in saliva in persons at increased risk for psychosis suggest that individuals with increased cortisol levels are more likely to develop psychosis (e.g. Walker et al., 2013). However, since the number of persons who developed psychosis was small, these findings remain preliminary. Analysis of HCC in patients presenting with an acute episode offers the potential to determine whether these individuals had increased cortisol during the three month period preceding admission, as compared to patients in remission and controls. This approach could shed light on the issue of whether increased cortisol is a state or a trait marker, i.e., whether cortisol is exclusively increased before the onset of an acute episode or whether it is also increased during remission. This approach could also be used to explore potential differences between BD and SCZ. For the purposes of the present study, this approach was used to assess HPA axis activity in BD and SCZ patients presenting with an acute episode or in remission, and in controls.

The main aim of the present study was to investigate whether BD and SCZ patients show differences in terms of perceived stress and HPA axis activity (as measured by HCC). We investigated whether perceived stress and HCC change over the disease course and differ between acute episode and remission, and whether these two stress measures, i.e., one subjective and one biological, are correlated. Furthermore, we explored whether an association exists between these two stress measures and an increased genetic risk for BD or SCZ.

2. Material and methods

2.1. Sample

Patients and controls were assessed at the Psychiatric Clinic, Clinical Center, University of Sarajevo, Bosnia and Herzegovina between 2011 and 2014. The study included in- and outpatients aged between 18 and 65 years with a diagnosis of SCZ or BD Bipolar I Disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and healthy control subjects, recruited from students and personnel from other (non-psychiatry) departments of the clinic, with neither a diagnosis of psychiatric disorder nor a family history of BD and SCZ. The study was approved by the respective local ethic committees in Bosnia and Herzegovina and in Germany. Written informed consent was obtained from all participants. Inpatients, who were admitted to the hospital in an acute phase, were included in the study on the basis of pre-informed consent. Final consent was obtained on remission, when the patients were able to make an informed decision.

The cohort comprised: (i) 77 SCZ inpatients and 82 SCZ outpatients; (ii) 38 BD inpatients and 23 BD outpatients; and (iii) 82 controls (for age and sex distribution, see Table 1). Subjects with somatic diseases that alter cortisol levels (endocrine diseases) were excluded. All subjects were of Bosnia and Herzegovina descent according to self-reported ancestry.

Inpatients were recruited from consecutive hospital admissions, and outpatients from the outpatient clinic. Lifetime best estimate diagnoses were assigned according to DSM-IV criteria. All diagnoses were assigned by a trained psychiatrist using information from multiple sources, including the Structured Clinical Interview