



Diurnal cortisol variation and cortisol response to an MRI stressor in schizophrenia and bipolar disorder



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ABSTRACT

Markers of HPA axis function, including diurnal cortisol rhythm and cortisol responses to stress or pharmacological manipulation, are increasingly reported as disrupted in schizophrenia (SZ) and bipolar disorder (BD). However, there has been no direct comparison of cortisol responses to stress in SZ and BD in the same study, and associations between cortisol dysfunction and illness characteristics remain unclear. In this study we used spline embedded linear mixed models to examine cortisol levels of SZ and BD participants at waking, during the first 45 min after waking (representing the cortisol awakening response; CAR), during the period of rapid cortisol decline post the awakening response, and in reaction to a stressor (MRI scan), relative to healthy controls (HC). Contrary to expectations, neither SZ nor BD showed differences in waking cortisol levels, CAR, or immediate post-CAR decline compared to HC; however, waking cortisol levels were greater in BD relative to SZ. In response to the MRI stressor, the SZ group showed a significant absence of the expected increase in cortisol responsivity to stress, which was seen in both the BD and HC groups. Clinical factors affecting the CAR differed between SZ and BD. In SZ, higher antipsychotic medication dosage was associated with a steeper incline of the CAR, while greater positive symptom severity was associated with a more blunted CAR, and greater levels of anxiety were associated with the blunted cortisol response to stress. In BD, longer illness duration was associated with a steeper incline in CAR and lower levels of waking cortisol. These results suggest that cortisol responses may normalize with medication (in SZ) and longer illness duration (in BD), in line with findings of aberrant cortisol levels in the early stages of psychotic disorders.

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1. Introduction

There is accumulating evidence of disrupted hypothalamic–pituitary–adrenal (HPA) axis function in psychosis (Bradley and Dinan, 2010). Cortisol is an endogenous corticosteroid that is released in response to stress, and regulated via negative feedback loops within the HPA axis (Hellhammer et al., 2009); within this system, cortisol levels typically follow a circadian rhythm whereby concentrations peak in the first hour after waking (cortisol awakening response, CAR), followed by a steep post-CAR decline, after which a more gradual decrease in

concentration continues throughout the remainder of the day (Edwards et al., 2001; Rea et al., 2012). In both schizophrenia (SZ) and bipolar disorder (BD), there is evidence of abnormally heightened morning cortisol levels compared to healthy controls (Girshkin et al., 2014), as well as abnormalities in the CAR (Aas et al., 2011; Mondelli et al., 2010; Monteleone et al., 2014) and greater diurnal variation in cortisol output (Cervantes et al., 2001; Gil-Ad et al., 1986; Gunduz-Bruce et al., 2007; Havermans et al., 2011; Monteleone et al., 1992; Whalley et al., 1989). Recent findings of blunted CAR in first episode psychosis (Aas et al., 2011; Mondelli et al., 2010; Pruessner et al., 2013b), and abnormal morning cortisol levels in ostensibly high-risk samples (Cullen et al., 2014; Ellenbogen et al., 2010; Karanikas et al., 2014; Sugranyes et al., 2012; Walker et al., 2013), suggest that dysregulated cortisol release may be an intermediate phenotype of psychosis (see also Duffy et al., 2012). However, the evidence for an abnormal CAR in SZ and BD has not been consistent (Cervantes et al., 2001;

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Deshauer et al., 2006; Hempel et al., 2010; Rao et al., 1995; Walder et al., 2000; Whalley et al., 1989), and disrupted circadian activity is not always reported (Bradley and Dinan, 2010; Fries et al., 2014; Deshauer et al., 2006).

In addition, blunted cortisol responses to psychological stress have been shown in both SZ (Ciufolini et al., 2014) and BD (Havermans et al., 2011; Houtepen et al., 2015; Wieck et al., 2013). This is particularly interesting in the context of emerging evidence of abnormal stress reactivity in first-episode psychosis and younger 'at-risk' samples, where several studies have now shown *heightened* (rather than blunted) stress responses in the earlier (or prodromal) stages of psychosis (Collip et al., 2011; Houtepen et al., 2015; Lincoln et al., 2015; Pruessner et al., 2013a; van Venrooij et al., 2012). Notably, these recent studies have examined cortisol reactivity in response to common, daily-life stress; however, no previous study has examined cortisol responses to a novel stressor (such as a magnetic resonance imaging [MRI] scan) in SZ or BD. We therefore set out to determine the evidence for disrupted diurnal cortisol responses in a chronic sample of cases with SZ or BD, in the context of exposure to an MRI scan as a novel stressor.

Stress responses evoked by MRI scanning in healthy individuals have been shown to be associated with increased cortisol levels (Muehlhan et al., 2011; Tessner et al., 2006) similar to that elicited by psychological stress tasks e.g., the Trier Social Stress Task (TSST; Kirschbaum et al., 1993). Most recently, a study that made use of the Montreal Imaging Stress Task (Dedovic et al., 2005) – a psychosocial stress task completed in an MRI setting – showed that psychotic participants experienced a significant increase in self-reported stress, and a stress induced increase in dopamine release (Mizrahi et al., 2012). However, no studies have examined cortisol responses to MRI exposure in psychotic disorders.

Regarding the effects of clinical features on HPA function, a recent meta-analysis highlights the influence of illness chronicity, medication status, mood state, and remission from psychosis on cortisol levels in SZ and BD (Girshkin et al., 2014). For example, evidence suggests that cortisol levels are heightened in depressive and euthymic phases of BD, but not mania (Girshkin et al., 2014; Havermans et al., 2011). In contrast, SZ participants characterized by more severe negative symptoms (e.g., blunted affect and motor activity) show lower morning cortisol levels and a more blunted awakening response compared to other SZ participants with less severe negative symptoms (Belvederi Murri et al., 2012; White et al., 2014). However, there have also been reports of an association between reduced cortisol and less severe negative symptoms in SZ (Iancu et al., 2007). Associations between symptom severity and cortisol levels may also be moderated by medication effects on HPA axis function, even in at-risk samples; indeed, the relationship between illness stage and cortisol level has been shown to diminish when accounting for psychotropic medication use (Cohrs et al., 2006; Girshkin et al., 2014; Popovic et al., 2007; Sugranyes et al., 2012).

In the present study we examined salivary cortisol levels collected at four time points across the day, in groups of participants with SZ, BD, and in healthy controls, in the context of a novel stressor (MRI scan) experienced on the day of saliva collection. Focal analyses investigated group differences in diurnal cortisol changes, including: 1) waking cortisol concentration, 2) the rise of cortisol levels during the CAR, and 3) the decline of cortisol levels during the period immediately following the CAR, as well as, 4) changes in cortisol levels in response to exposure to an MRI scan later that same day. Associations between indices of HPA function and symptom severity, illness length and medication dosage on the day of the scan were also investigated. It was hypothesized that, relative to healthy controls, both SZ and BD participants would show greater levels of cortisol at waking, a blunted CAR, a faster rate of cortisol level decline post awakening response, and dampened cortisol stress

reactivity. Further, it was expected that heightened cortisol levels at waking, and a blunted CAR, would be associated with increased symptom severity, longer illness duration, and lower medication dosage in SZ and BD. We further expected that levels of state anxiety, as measured on the morning of the scan, would be associated with cortisol responses to stress in all participant groups.

2. Methods

This research was approved by the Human Research Ethics Committees of the University of New South Wales (HREC UNSW Protocol No. 12384), the South Eastern Sydney–Illawarra Area Health Service (SESIAHS Protocol No. 09/081), and St. Vincent's Hospital (HREC/10/SVH/92); All participants provided written informed consent to participate in the study.

2.1. Participants

Participants were 59 healthy controls (HC; mean age = 34.87, SD = 11.79), 56 cases diagnosed as bipolar-I disorder (BD; mean age = 37.21, SD = 12.07), and 56 cases diagnosed with either schizophrenia ($n = 38$) or schizoaffective disorder ($n = 18$) that were grouped together (SZ; mean age = 42.81, SD = 11.53). Clinical participants were recruited from outpatient psychiatric services of the South Eastern Sydney–Illawarra Health District, St. Vincent's Hospital, the Sydney Bipolar Disorders Clinic (Mitchell et al., 2009), the Australian Schizophrenia Research Bank (ASRB; Loughland et al., 2010) and advertisements via consumer support networks. Healthy controls were recruited via advertisements in the general community. Exclusion criteria were head injuries resulting in loss of consciousness, substance abuse or dependence in the last six months, epilepsy, or central nervous infections. Trained research staff confirmed clinical diagnoses according to ICD-10 criteria, using the OPCRIT algorithm applied to responses on the Diagnostic Interview for Psychosis–Diagnostic Module (DIP-DM; Castle et al., 2006; McGuffin et al., 1991); the DIP also provides extensive information on drug and alcohol use. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to screen for the presence of DSM-IV Axis I disorders and substance abuse in control participants.

2.2. Materials

2.2.1. Clinical assessment

Symptom severity of clinical participants was assessed using the Young Mania Rating Scale (YMRS; Young et al., 1978), the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), and the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The State/Trait Anxiety Inventory (STAI; Spielberger et al., 1970) was used to measure anxiety levels on the morning of the magnetic resonance imaging (MRI) scan. Illness phase of BD participants was categorized using the Internal State Scale (ISS; Bauer et al., 1991).

2.3. Procedure

2.3.1. Saliva collection

Saliva collection was undertaken using pre-labeled Salivettes (Sarstedt, Sydney, Australia) provided to participants with written instructions to collect two saliva samples at home, in the morning of the day of their scheduled testing appointment: the first upon waking, and another 45 min later. Participants were requested to refrain from smoking, brushing their teeth, and eating or drinking for thirty minutes before collecting these salivary samples, and instructed to keep their samples in their home refrigerators (Garde and Hansen, 2005) until leaving for their appointment. Each participant was also

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