



Longer-term increased cortisol levels in young people with mental health problems

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ABSTRACT

Disturbance of hypothalamus–pituitary–adrenal axis activity is commonly reported in a range of mental disorders in blood, saliva and urine samples. This study aimed to look at longer-term cortisol levels and their association with clinical symptoms. Hair strands of 30 young people (16–25 years) presenting with mental health problems ($M_{\text{age}} \pm SD = 21 \pm 2.4$, 26 females) and 28 healthy controls (HC, $M_{\text{age}} \pm SD = 20 \pm 2.9$, 26 females) were analyzed for cortisol concentrations, representing the past 6 months prior to hair sampling. Clinical participants completed an assessment on psychiatric symptoms, functioning and lifestyle factors. All participants completed the Perceived Stress Scale. Hair cortisol concentrations representing the past 3 (but not 3–6) months were significantly increased in clinical participants compared to HC. Perceived stress in the past month was significantly higher in clinical participants compared to HC, but not significantly correlated with hair cortisol. Hair cortisol levels were not significantly associated with any other measures. Hair segment analyses revealed longer-term increased levels of cortisol in the past 3 months in early mental health problems. Further insight into the role of cortisol on the pathogenesis of mental illnesses requires longitudinal studies relating cortisol to psychopathology and progression of illness.

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1. Introduction

Disturbances in hypothalamus–pituitary–adrenal (HPA) axis diurnal activity and responsivity are common findings in a range of mental disorders (e.g. Yehuda et al., 1993; Meewisse et al., 2007; Knorr et al., 2010). One of the most commonly reported parameters of the HPA axis is the glucocorticoid hormone cortisol. Over- and under-activity of cortisol concentrations have been reported by means of blood, saliva and urine samples in mood disorder (Cervantes et al., 2001; Vreeburg et al., 2009), psychosis (Ryan et al., 2004), posttraumatic stress disorder (PTSD) (Yehuda et al., 1990), panic (Bandelow et al., 2000) and generalized anxiety disorder (GAD) (Mantella et al., 2008), somatization syndrome (Rief et al., 1998), and eating (Monteleone et al., 2001) and substance use (Adinoff et al., 2003) disorders. Despite this, there is considerable variability across (Yehuda et al., 1993) and within diagnostic categories (for meta-analyses in PTSD, see Meewisse et al. (2007), and depression, see Knorr et al. (2010)), which is why

it is important to investigate whether cortisol fluctuations can be explained by factors other than specific diagnostic categories, such as inter-individual differences and stressor characteristics (Miller et al., 2007).

Established analyses of cortisol in *saliva*, *plasma* and *urine* have proven to be useful and reliable tools for documenting *real-time* circulating cortisol levels (*plasma*, *saliva*) or mean cortisol excretions over a specific time, usually 24 h (*urine*). In contrast, *hair* cortisol represents a reliable, *longer-term* measure (generally up to months) of stress and endogenous cortisol concentrations (Stalder and Kirschbaum, 2012). The advantages of hair cortisol assessment lie in providing a retrospective examination of hair cortisol levels over an extended time period that is virtually impossible to achieve with other methods. Moreover, it is a non-invasive sampling method, samples can be easily stored at room temperature for an extended period, and sampling avoids problems of adherence which often experienced with other methods. However, hair cortisol concentrations decrease from more proximal to distal segments in human scalp hair, limiting the retrospective period of examination (Stalder and Kirschbaum, 2012).

Considering a generally accepted human scalp hair growth rate of 1 cm per month (Wennig, 2000) and taking hair samples from the scalp near the posterior vertex region, this method allows for

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retrospective capture of cortisol concentrations for up to six months (Dettenborn et al., 2012). Recent studies in clinical populations have demonstrated increased hair cortisol concentrations in depression (Dettenborn et al., 2012), PTSD (Steudte et al., 2011a), and in alcohol-dependent individuals (Stalder et al., 2010), and decreases in GAD (Steudte et al., 2011b), and PTSD (Steudte et al., 2013). Occupational impairment (i.e. unemployment) has also been shown to be associated with increased hair cortisol (Dettenborn et al., 2010). Strong test–retest associations for repeated hair cortisol measurements have been revealed, indicating high intra-individual stability. Structural equation modelling showed that, if no major life events or other stressors are present, hair cortisol assessments comprise a strong trait component which explains between 59% and 82% of variance in cortisol levels (Stalder et al., 2012). A recent systematic review of hair analyses revealed variations in hair cortisol (Staufenbiel et al., 2013) that are similar to findings from meta-analyses and reviews on more established cortisol measures (Meewisse et al., 2007; Knorr et al., 2010). Despite some inconsistencies, hair cortisol appears to be increased in depression, and decreased in anxiety disorders (Staufenbiel et al., 2013).

The period of adolescence and young adulthood is characterized by increased vulnerability for the development of mental disorders. Half of the lifetime cases of mental disorder start by age 14 and three quarters by age 24 (Kessler et al., 2005). It is hypothesized that adolescence is accompanied by a biological sensitivity to stress and that age-related cortisol increase may trigger the expression of symptoms in vulnerable individuals (Walker et al., 2010). Higher cortisol levels predict a higher risk of conversion to psychotic disorder in at-risk individuals, providing support for this hypothesis (Walker et al., 2010). The pathogenesis of childhood anxiety disorders appears similar: high levels of cortisol may induce changes to subcortical circuits, which may make children vulnerable to developing anxiety symptoms (Muris, 2006). In one study, Rao et al. (2008) exposed adolescents with depressive disorder and healthy controls (HC) to psychosocial stress. Both groups showed increased cortisol levels, but individuals with depression displayed an increased and sustained cortisol response. This supports the notion that stressful events play a role in the development and maintenance of depressive symptoms (Rao et al., 2008).

The time between the onset of the disorder (or stressful or traumatic event) and hair collection appears to be a crucial element in explaining the diversity of cortisol findings. Luo et al. (2012) reported increased hair cortisol one month after a traumatic event in adolescents with PTSD, with levels decreasing after 7 months (for review, see Staufenbiel et al. (2013)). Increased cortisol levels are therefore likely to reflect the on-going stress and not the disorder itself (Staufenbiel et al., 2013). A significant difference was observed between early- and late-onset bipolar disorder. Patients with a late onset disorder (≥ 30 years) presented with higher hair cortisol than the early-onset group and HC (Manenschijs et al., 2012). This finding suggests that early onset bipolar disorder may be more strongly linked to a genetic vulnerability while late onset is usually triggered by life events and stress (Staufenbiel et al., 2013). Taken together, these findings suggest that HPA axis activity is elevated at the time of stressor onset with declining cortisol levels as time passes (Miller et al., 2007). However, the exact timeline of these hormonal changes is unclear; that is, how long does the hypothesized cortisol increase persist?

An alternative to explaining the heterogeneity of HPA axis findings by classifying mental ill health into disorder-specific categories is to use a dimensional approach. In this way, one can examine symptom severity and consider a timeline of an individual's symptoms. One example of a dimensional approach is a

clinical staging model. Within this framework, mental disorders are assumed to develop from a *pluripotential state*, consisting of undifferentiated general symptoms (such as depressive and anxiety symptoms), and from a background of specific and non-specific risk factors (McGorry et al., 2006; Lin et al., 2013), which are associated with non-specific distress (McGorry, 2013). This idea is supported by the recent finding of a common mental distress factor underlying depressive, anxiety, and psychotic phenomena in adolescents (Stochl et al., 2015). It can therefore be inferred from the clinical staging model that the early stages of mixed mental health problems are likely to coincide with elevated cortisol levels. However, to our knowledge, there has been no study investigating longer-term cortisol levels in youth with early mental health problems from a clinical staging perspective.

The aim of this study was to investigate the pathogenesis of mental disorders in adolescents and young adults, and whether diverse psychiatric symptoms are associated with altered longer-term cortisol levels. We included young people who had sought help for mental health problems, as well as HC. We wanted to test the hypothesis that early stages of mental health problems are associated with significant distress (McGorry, 2013) and therefore elevated cortisol levels. We further explored the association between cortisol levels and general psychological distress, depressive, anxiety and psychotic symptoms, alcohol and tobacco use, and childhood traumatic experiences.

2. Methods

2.1. Participants

Thirty-one participants seeking help for mental health problems were recruited from the South Birmingham area via clinical services (Youthspace & Birmingham Healthy Minds). Inclusion criteria were being aged 16–25 years and recently help-seeking (within 6 months of clinical contact) for mental health problems. Youthspace is a youth-focused secondary mental health service that provides support for youth aged 16–25 years. The service sees young people with a variety of diagnoses and has no specific exclusion criteria. Youthspace offer a variety of treatments and case management is provided by a multi-disciplinary team. Birmingham Healthy Minds is a primary care psychological therapy service, offering brief psychological talking therapy for individuals aged 16 and above who present with depressive and anxiety symptoms. Their exclusion criteria are bipolar disorder, psychosis, suicidality or need for long-term care. At the time of recruitment, both services operated primarily through GP referral. All clinical participants from both services were generally eligible for the study. Participants were recruited in one of three ways: (1) via their clinician; (2) approached by the researcher in the waiting room before or after their appointment at Youthspace; or (3) by responding to a poster advertisement at these services. Not all eligible individuals at the services were approached for participation. Reasons for this are because their clinicians may not have felt that participation was appropriate (e.g. they were in crisis), or because a researcher was not at the clinic on the days of their appointments. Both services operated via multiple clinicians at multiple sites, and therefore due to practical reasons, it was not possible to gather statistics on refusal rates. However, not all service users who were initially approached took part in the study. Obtaining consent to partake meant in the first instance, taking part in an interview and self-report study focusing on mental health symptoms, functioning and general life style factors. In the second instance, individuals who either had a family history with mental health problems in a first-degree relative or who subjectively did not improve concerning their well-being after six

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