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Associations between diurnal cortisol patterns and lifestyle factors, psychotic symptoms, and neurological deficits: A longitudinal study on patients with chronic schizophrenia

Rainbow T.H. Ho [a, b, *], Ted C.T. Fong [a], Adrian H.Y. Wan [a], Friendly S.W. Au-Yeung [c], Eric Y.H. Chen [d], David Spiegel [e]

[a] Centre on Behavioral Health, The University of Hong Kong, Hong Kong
[b] Dept of Social Work & Social Administration, The University of Hong Kong, Hong Kong
[c] The Providence Garden for Rehab, Hong Kong Sheng Kung Hui Welfare Council Limited, Hong Kong
[d] Dept of Psychiatry, The University of Hong Kong, Pokfulam, Hong Kong
[e] Dept of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

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ABSTRACT

The present study examined the relationships between diurnal cortisol patterns and perceived stress, lifestyle factors, psychotic symptoms, neurological deficits, and daily functioning in patients with chronic schizophrenia. The participants were 149 Chinese patients with chronic schizophrenia, who provided salivary cortisol measures upon waking, before lunchtime, and before bedtime at baseline (Time 1). Self-report measures on perceived stress and lifestyle factors such as body-mass index and daily exercise span were recorded at Time 1. Diagnostic assessments on psychotic symptoms, neurological deficits, and daily functioning were made at Time 1 and Time 2 (3 months later). Latent growth modeling and path modeling analysis were performed to investigate the diurnal cortisol patterns and the relationships with the study variables, respectively. Greater perceived stress and body-mass index and less physical activity were significantly linked to reduced cortisol decline. Reduced cortisol decline at Time 1 significantly predicted greater psychotic (positive and negative) symptoms and more severe neurological deficits in motor coordination and sequencing of complex motor acts at Time 2. The present results contribute to a better understanding of the diurnal cortisol patterns among chronic schizophrenia patients and the associations with lifestyle factors, psychotic symptoms, and neurological deficits. The findings lend support to the neural diathesis–stress model and suggest that hypothalamic–pituitary–adrenal axis may potentially mediate the effects of lifestyle factors on psychotic symptoms and neurological deficits.

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine system that plays a central role in coordinating the stress response via the secretion of cortisol, a major steroid, to maintain homeostasis in various physiological systems (Gunnar and Quevedo, 2007). In normal individuals, cortisol levels display a typical circadian rhythm with an early morning peak upon waking, followed by a gradual decline throughout the day, and a rise during sleep (Turner-Cobb, 2005). Cortisol levels upon waking reflect basal cortisol without exposure to stressors and the diurnal cortisol slope reflects the fluctuation of cortisol levels throughout the day (Smyth et al., 1997). Evaluation of the circadian cortisol fluctuation is indicative of the HPA axis reactivity.

Schizophrenia is a neuropsychiatric disorder that is attributable to multiple biological and environmental factors. The neural diathesis–stress model (Walker and Diforio, 1997) is widely adopted to explain how environmental stressors interact with preexisting biological vulnerability in the etiology of the disorder. This model proposes that psychosocial stress acts via the HPA axis to trigger or worsen the schizophrenic symptoms (Walker et al., 2004). Persistent stress exposure can lead to chronic elevations in cortisol release and impair the negative feedback system that dampens HPA activity (Walker et al., 2008). These could lead to over activation in

* Corresponding author. Centre on Behavioral Health, 2/F, The Hong Kong Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong.
E-mail address: tinho@hku.hk (R.T.H. Ho).

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dopamine pathways and hyperactivity in dopamine neurotransmission (Dallman et al., 2004; Moghaddam, 2002), which could result in exacerbation of the psychotic symptoms.

Compared with healthy controls, patients with schizophrenia manifest evident damage in the hippocampus, a brain region that regulates HPA activity via glucocorticoid receptors (Harrison, 2004). Heightened baseline cortisol and flattened diurnal curves in terms of reduced cortisol decline have been associated with greater symptom severity, poorer cognitive performance, and memory deficits in the patients (Goyal et al., 2004; Hempel et al., 2010; Ko et al., 2007; Lupien et al., 2005; Walder et al., 2000; Yilmaz et al., 2007). Despite the relationships between heightened cortisol and various prognostic indicators in schizophrenia, few studies have examined the prognostic value of the diurnal cortisol slope in mediating symptoms caused by stress exposure.

Patients with chronic schizophrenia have shown HPA axis dysfunctions (Kaneko et al., 1992), heightened negative symptoms, and ill-health such as metabolic syndrome, diabetes mellitus and premature mortality (Bradley and Dinan, 2010; Gury, 2004; Laursen, 2011; Ryan and Thakore, 2002). Compared with patients with first-episode psychosis, chronic schizophrenia patients in general receive long-term treatment of antipsychotic medications. Antipsychotic treatment has shown dampening effects on HPA activation and normalizes diurnal cortisol hyper-secretion in schizophrenia patients (Mondelli et al., 2010; Walker et al., 2008). In particular, atypical antipsychotic medications have been found to produce significant improvements in clinical outcomes and HPA axis functioning over typical antipsychotic treatment in previous studies (Altamura et al., 1999; Cohrs et al., 2006; Zhang et al., 2005).

Current research literature on schizophrenia focuses on its developmental course among first-episode or high-risk samples (Carol and Mittal, 2015; Cullen et al., 2014; Simeonova et al., 2015). Though these studies have contributed to a better understanding of its etiology and predictors of illness onset, given the high relapse rate and chronicity, it is essential to identify potential risk and protective factors of its long-term prognosis (Breier et al., 1991). Factors associated with a healthy lifestyle, namely, maintaining a normal body mass index (BMI) and being physically active, have been identified as predictors of better prognosis during antipsychotic treatments (Brown et al., 1999; Manzanares et al., 2014). Yet, research on the associations between the lifestyle factors and diurnal cortisol patterns in patients with chronic schizophrenia has been scarce.

The present longitudinal study aimed to investigate the associations between diurnal cortisol patterns and lifestyle factors, symptom severity, neurological deficits, and daily functioning in patients with chronic schizophrenia. The first hypothesis was that higher levels of perceived stress contribute to HPA axis dysfunctions. The second hypothesis was that HPA axis dysfunctions predict greater psychotic symptoms and neurological deficits, and poorer daily functioning. The third hypothesis was that lifestyle factors (BMI and physical activity) are significantly associated with diurnal cortisol patterns. The present study took into account the influences of chronicity and antipsychotic treatment as likely confounding factors of the HPA axis activity. Fig. 1 shows the conceptual model of the present study.

2. Methods

2.1. Participants

The present study adopted a longitudinal study design and recruited 149 patients with chronic schizophrenia who were institutionalized in a mental health rehabilitation complex in Hong Kong in January 2014 (Time 1). The data analyzed in this study originated from a randomized controlled trial of Taichi and exercise interventions on chronic schizophrenia patients. The rehabilitation complex provides long-term care and halfway house services to the patients. The inclusion criteria of the participants were fulfillment of the DSM IV-TR criteria for schizophrenia as diagnosed by a psychiatrist, aged 18–65 years, and ability to understand and speak Cantonese. The exclusion criteria included relapses in schizophrenia that required hospitalization, suffering from severe schizophrenic symptoms (such as persistent withdrawal) that would limit their ability to interact in the assessment interview, a history of organic mental disorder, i.e. decreased mental function due to a medical disease (such as delirium, dememtia, or brain trauma) other than a psychiatric illness, presence of physical disabilities or other severe illnesses that may impair cognitive or visuo-motor functioning. The participants completed follow-up assessments on psychotic and neurological symptomatology as well as daily functioning three months later (Time 2).

2.2. Procedures

The study was carried out in accordance with the latest version of the Declaration of Helsinki and the study design was reviewed by the local institutional review board. Written informed consent was obtained from the participants after the nature, risks, and benefits of the study procedures had been fully explained during the screening interview. The participants completed a saliva collection protocol, a self-report questionnaire on daily functioning and diagnostic assessments on psychiatric symptoms and neurocognitive deficits. Their heights and weights were measured to compute the body mass index (BMI, kg/m^2) with the following cut-off limits for Asians: underweight (<18.5), normal (18.5–22.9), overweight (23.0–27.5), and obese (>27.5) (WHO, 2004). In addition to demographic characteristics (age, gender, education level, and marital status) and daily exercise spans, data on medication was collected from the patients' personal record which provided information on the type of antipsychotic medications received by the participants, duration of psychiatric diagnosis, and their medication dosage.

2.3. Salivary cortisol assessment

Written instructions and verbal explanations were provided to the participants on collection of saliva samples using cotton salivette tubes in the hostel at three occasions at Time 1: upon waking, before lunch and before bedtime. Since the participants were residing in the institution, they followed a stable daily routine and fixed meal schedule. They were reminded to collect the first saliva sample immediately upon awakening, to avoid food consumption for 30 min prior to sample collection, and to avoid strenuous exercise to avoid distorting the results. To improve adherence to the collection protocol, we provided instruction sheets and briefing sessions for the ward attendants on the day of data collection. The participants were instructed to record their time of collection of each sample on a time sheet that provided the sampling instructions. The collected salivette tubes were kept frozen at the laboratory. Cortisol levels were determined after thawing and centrifugation at 3000 rpm for 15 min using the ELISA kit (Salimetrics, PA, USA). The intra-assay and inter-assay variation was less than 10%. Of the 447 collected saliva samples, 414 (92.6%) provided valid cortisol values. Data analyses were based on 399 of the 414 valid samples (96.4%) after screening for outliers (>3 SD deviations from the mean). The diurnal cortisol slope was used in this study as the main summary variable for the cortisol measures. To provide a more thorough description of the diurnal cortisol pattern, we also calculated the mean cortisol level as the average of the three