Schizophrenia Research 172 (2016) 29–34

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The relations of age and pubertal development with cortisol and daily stress in youth at clinical risk for psychosis

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ARTICLE INFO

Article history:
Received 6 November 2015
Received in revised form 28 January 2016
Accepted 1 February 2016
Available online 20 February 2016

Keywords:
Schizophrenia
Psychosis
Puberty
Stress
Cortisol
Clinical high risk

ABSTRACT

Background: Prodromal syndromes often begin in adolescence — a period of neurodevelopmental changes and heightened stress sensitivity. Research has shown elevated stress and cortisol in individuals at clinical high risk (CHR) for psychosis. This cross-sectional study examined relations of age and pubertal status with cortisol and self-reported stress in healthy controls (HCs) and CHR adolescents. It was hypothesized that the relations of age and pubertal stage with cortisol and stress would be more pronounced in CHR youth.
Methods: Participants were 93 HCs and 348 CHR adolescents from the North American Prodrome Longitudinal Study (NAPLS). At baseline, measures of stress (Daily Stress Inventory — DSI), Tanner stage (TS), and salivary cortisol were obtained.
Results: ANCOVA revealed increased DSI scores with age for both groups, and higher DSI scores in CHR adolescents than HCs, with a more pronounced difference for females. Contrary to prediction, with age controlled, HCs showed greater TS-related DSI increases. Analysis of cortisol showed no significant interactions, but a main effect of age and a trend toward higher cortisol in the CHR group. Correlations of cortisol with TS were higher in HC than CHR group.
Conclusions: Stress measures increased with age in HC and CHR adolescents, and DSI scores also increased with TS in HCs. The results do not support a more pronounced age or TS increase in stress measures in CHR adolescents, but instead suggest that stress indices tend to be elevated earlier in adolescence in the CHR group. Potential determinants of findings and future directions are discussed.

1. Introduction

Vulnerability to psychotic disorders is assumed to be congenital (Dempster et al., 2011), but its expression appears to be triggered by environmental factors, including stressful events (Dvir et al., 2013). It has been proposed that the adverse effects of stress exposure on vulnerable individuals are partially mediated by the consequent increase in activation of the hypothalamic pituitary–adrenal (HPA) and elevated cortisol secretion (Walker et al., 2008). In addition, independent of stress, there is evidence that normal neuromaturational processes augment stress

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http://dx.doi.org/10.1016/j.schres.2016.02.002
0920-9964/

and cortisol levels during adolescence, and it has been suggested that these processes increase risk for onset of the prodrome to serious mental disorders, including psychosis (Trotman et al., 2013; Walker et al., 2008). Specifically, the risk for psychosis onset rises dramatically following age 13, and increases with each year of age through adolescence (de Girolamo et al., 2012; Thorup et al., 2007). In clinical high risk (CHR) samples, the prodromal syndrome shows a similar trend, and appears to predate psychosis onset by about a year (Chung et al., 2010).

1.1. Adolescent development and stress

Research on normal adolescents has demonstrated that self-reported stress and psychiatric symptoms increase with age and pubertal stage (De Vriendt et al., 2011; Lenroot and Giedd, 2010; Oldehinkel et al., 2011; Rudolph, 2008; Sumter et al., 2010). Similarly, basal cortisol increases with both age and pubertal development in healthy adolescents (Sinclair et al., 2014; Gunnar et al., 2009; Kiess et al., 1995; Matchock et al., 2007; Netherton et al., 2004). These findings are consistent with the generalized increase in risk for onset of behavioral disorders during adolescence/young adulthood, as well as the notion that the biological systems involved in the stress response, including the HPA axis, may play a role in triggering the expression of vulnerability (Walker et al., 2008).

While activation of the HPA axis in response to stress is adaptive, prolonged cortisol elevations may compromise brain function, which can then contribute to dysregulation of the HPA axis and the emergence of psychiatric symptoms (Herbert et al., 2006; Zhu et al., 2014). Also, independent of stress exposure, the normative rise in cortisol during adolescence may increase susceptibility to psychiatric disorders in vulnerable individuals (Quevedo et al., 2009; Sontag-Padilla et al., 2012). It has been suggested that increased HPA activation following the onset of puberty may increase susceptibility for a range of psychiatric syndromes, including psychosis (Trotman et al., 2013).

In recent years, the focus of research on stress and psychotic disorders has shifted toward the prodromal phase; individuals who meet standardized criteria for the prodrome are designated as CHR, and the estimated rate of conversion to psychosis in this group ranges from 20 to 40% (Larson et al., 2010). Because prodromal syndromes most often arise in adolescence/young adulthood, CHR studies focus on this transitional stage (Addington and Heinssen, 2012).

To date, findings from CHR research generally parallel those from studies of psychotic patients. For example, CHR individuals report more stress than healthy controls (HCs) (Cullen et al., 2014; Pruessner et al., 2011). In a report based on the first half of the North American Prodrome Study (NAPLS-2) cohort, aged 13 to 30 years, CHR subjects reported more daily stress than HCs, and the CHR subjects who subsequently converted to psychosis reported greater stress than remitted CHR subjects, with those who remained prodromal falling in between (Trotman et al., 2014). Also, of interest to note, there was a trend for a more pronounced relation between stress and age for the CHR group.

With regard to stress biomarkers, there is evidence that CHR subjects manifest heightened basal cortisol (Shah and Malla, 2015). Another recent report on the first-half cohort from NAPLS-2, again with subjects ranging from 13 to 30 years, indicated that both HCs and CHR subjects manifested an age-related increase in cortisol through this period (Walker et al., 2013). Further, heightened basal cortisol was found in CHR individuals when compared to HCs, and those CHR participants who later converted showed higher levels than those who remitted, but not those who continued to meet prodromal criteria.

While pubertal development is associated with increased stress and cortisol in healthy adolescents, the relation of pubertal stage with these variables in CHR adolescents has not yet been examined. Some have proposed that the clinical expression of the prodrome to psychosis typically arises in adolescence because it is triggered by abnormalities in the timing and/or magnitude of postpubertal neuromaturational processes (Keshavan et al., 2014; Trotman et al., 2013). It is possible that, when compared to HCs, CHR adolescents manifest a more pronounced increase and/or an earlier onset of rising stress indices with the progression of puberty, and that this contributes to risk for psychosis. The present study addresses this issue by examining the relations of age and pubertal stage with stress and cortisol levels in youth from NAPLS-2. The complete sample from this multi-site, prospective study now includes over 700 CHR and 200 HC subjects, and a measure of Tanner stage (TS) was administered to all of those under 19 years of age. Thus, there are now enough subjects in the 13 to 19 year age-range to examine TS. Based on the evidence that both stress indices and prodromal/psychotic symptoms increase through the adolescent years, and that age-related increases in stress may be greater for CHR subjects (Trotman et al., 2014), it is hypothesized that CHR youth will show a more pronounced relation of age and Tanner pubertal stage with self-reported daily stress and basal cortisol.

2. Experimental/materials and methods

2.1. Sample

Participants were drawn from the completed cohort of 764 CHR participants and 280 HCs in NAPLS-2 (Addington and Heinssen, 2012). The present subsample includes all participants, aged 13 to 18, for whom baseline data on TS, and self-reported stress and/or salivary cortisol were obtained; 348 CHR youth and 93 HCs. (Degrees of freedom vary in the analyses, as presented below, due to missing data on one of the dependent measures for some subjects.) Approximately 50% of these adolescents were included in the previous reports on stress and cortisol in the entire first half (13–30 years) of the NAPLS-2 sample. Demographic data on the present sample are presented in Table 1.

Exclusion criteria for both groups were substance dependence, neurological disorders, serious head trauma, IQ less than 70, and meeting DSM-IV criteria for a psychotic disorder, currently or in the past. For the HCs, those with a first-degree relative with psychosis or who met prodromal criteria were excluded. Details on sample characteristics and study procedures are presented in previous reports on NAPLS-2 (Addington and Heinssen, 2012; Walker et al., 2013).

2.2. Assessment procedures and measures

Sites screened participants using the Structured Interview for Prodromal Syndromes (SIPS), and diagnosed CHR participants based on the Scale of Prodromal Syndromes (SOPS) at baseline (Miller et al., 2003). The Structured Clinical Interview for DSM-IV Disorders was used to diagnose Axis I disorders (First et al., 2002).

2.3. Salivary cortisol

Details about NAPLS-2 saliva collection and cortisol assay procedures are presented in a previous report (Walker et al., 2013). In brief, dietary

Table 1
Demographic and clinical characteristics.

	Healthy controls N = 348	CHR N = 93
Baseline age M (SD), n		
Males	14.93 (1.83), 60	15.78 (1.72), 196
Females	15.63 (1.81), 33	15.36 (1.61), 152
Tanner total Male score M (SD)	8.18 (1.95)	8.26 (1.64)
Tanner total Female score M (SD)	7.67 (1.88)	7.25 (1.65)