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The Trier Social Stress Test in first episode psychosis patients: Impact of perceived stress, protective factors and childhood trauma

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ABSTRACT

Psychosis has been associated with abnormalities in hypothalamic-pituitary-adrenal axis functioning, which may emerge through heightened stress sensitivity following early life adversity – ultimately resulting in illness onset and progression. The present study assessed cortisol levels during an established psychosocial stress task and their association with current stress perception, putative protective factors and adverse childhood experiences in patients with a first episode of psychosis (FEP).

A total of 100 volunteers participated in the study, 57 of whom were patients with a FEP (mean age 23.9 ± 3.8) and 43 healthy community controls (mean age 23.2 ± 3.9). Salivary cortisol, heart rate and blood pressure were measured at eight time points before and after the Trier Social Stress Test. Subjective stress and protective factors were assessed with the Perceived Stress Scale, the Self-Esteem Rating Scale and the Brief COPE. Early life adversity was assessed with the Childhood Trauma Questionnaire.

Patients compared to controls showed significantly lower cortisol levels ($F = 7.38$; $p = .008$) throughout the afternoon testing period, but no difference in the cortisol response to the TSST. Heart rate was elevated and protective factors were lower in patients compared to controls. Attenuated cortisol levels were associated with higher levels of perceived stress, poor protective factors and more physical neglect during childhood.

Our results suggest that attenuated baseline cortisol levels and not a blunted response during an acute stress task might be an indicator of heightened stress vulnerability and poor resilience in psychosis. The possible influence of childhood adversity and antipsychotic medication is discussed.

1. Introduction

Accumulating evidence provides support for the notion that hypothalamus-pituitary adrenal (HPA) axis function, a key pathway of physiologic stress response, is dysregulated in schizophrenia and related psychoses (Pruessner et al., 2017; Walker et al., 2008; Walker and Diforio, 1997). While baseline cortisol levels have been shown to be elevated in psychosis in many studies (Borges et al., 2013; Yildirim et al., 2011), our group and others have shown that the cortisol response to awakening is rather blunted compared to healthy controls (Mondelli et al., 2010; Pruessner et al., 2008, 2013b). Research on the cortisol response to acute psychosocial stress suggests a similar blunting in psychosis patients (Brenner et al., 2009; Jansen et al., 2000; Lange et al., 2017b). While antipsychotic medication may play a role in elevating basal cortisol and diminishing the cortisol response to stimulation (Houtepen et al., 2015; Pruessner et al., 2017), a blunted HPA axis response to a public speaking task was also observed in unmedicated first episode psychosis (FEP) patients (van Venrooij et al., 2012) and in our own study with medication naïve individuals at clinical high risk for psychosis (Pruessner et al., 2013a). In the latter study, not only the cortisol response to the TSST was attentuated, but cortisol levels throughout the afternoon testing period were lower in patients compared to healthy controls (Pruessner et al., 2013a).

The neural diathesis-stress hypothesis in schizophrenia proposes that these alterations in HPA axis function are a consequence of the interaction between increased vulnerability and subsequent stress or adversity, ultimately promoting psychosis onset and progression through effects on dopaminergic function (Pruessner et al., 2017;

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Walker and Diforio, 1997). Particularly childhood trauma is increasingly seen as an important causal factor in the development of mental health problems such as psychosis (Fisher et al., 2013; Misiak et al., 2017; Varese et al., 2012). Here, it has been proposed that the underlying mechanism for the association between childhood adversity and psychosis might be a heightened sensitivity to subsequent social stress (van Winkel et al., 2008; Veling et al., 2016). Such sensitization might be reflected in elevated emotional and behavioural stress responses (Rauschenberg et al., 2017; van Nierop et al., 2018; Veling et al., 2016) as well as a re-programming of HPA axis responses to stress (Champagne, 2013; Liu et al., 1997; van Winkel et al., 2013).

Consistent with the notion of a heigthended stress sensitivity, levels of perceived stress have been shown to be elevated in patients with psychosis and to be associated with greater symptom severity (Millman et al., 2018; Pruessner et al., 2011; van Winkel et al., 2008). At the same time, factors that can serve as buffers towards the effects of stress exposure, such as social support (Gayer-Anderson and Morgan, 2013; Norman et al., 2005; Sundermann et al., 2014), self-esteem (Ciufolini et al., 2015; Vracotas et al., 2012) and active coping with stress (Moritz et al., 2016; Sellers et al., 2018), are frequently diminished in psychosis and associated with higher symptom severity. We recently also found such associations in individuals at clinical high risk for pychosis (Pruessner et al., 2011).

Altered HPA axis function following adverse childhood experiences has been observed in healthy individuals. Here, the majority of studies report reduced cortisol levels to psychosocial stress (Bunea et al., 2017), although others found no association between trauma and the neuroendocrine response to the Trier Social Stress Test (TSST) (DeSantis et al., 2011). Interestingly, there is little research on the association between early life adversity and HPA axis function in psychosis. Whereas childhood sexual abuse has been shown to be related to a higher cortisol awakening response (Mondelli et al., 2010), poor parental bonding during childhood was associated with blunted cortisol levels following awakening in psychosis patients (Pruessner et al., 2013b). Only one study up to now has investigated the association between childhood trauma and the cortisol response to the acute psychosocial stress in psychosis (Lange et al., 2017b). In this study, a modified version of the TSST was applied in 25 chronically ill patients with established schizophrenia spectrum disorder and a matching number of healthy controls. As with previous findings, the authors observed a blunted cortisol response to the TSST in patients compared to controls. Interestingly, when separating the patient group into those who did show a cortisol response (responders) and those who did not show a cortiol response to the TSST (non-responders), they found that responders had experienced higher levels of emotional abuse. This finding is somewhat unexpected considering that, as outlined above, both psychosis and childhood trauma have been associated with attenuated cortisol stress responses.

Clearly, a more comprehensive examination of the associations between alterations in neurobiological stress responses and psychological factors detemining stress sensitivity is required. Previous studies on the cortisol response to psychosocial stress included rather small numbers of mostly chronic psychosis patients (Brenner et al., 2009; Jansen et al., 2000; Lange et al., 2017b; van Venrooij et al., 2012). Our own previous study was conducted in patients at clinical high risk for psychosis (Pruessner et al., 2013a). While a variety of psychosocial stress tasks have been employed in previous studies, the TSST represents the best evidenced and most ecologically valid laboratory based stressor (Dickerson and Kemeny, 2004; Jones and Fernyhough, 2007) under which to investigate these assocations.

Given the shortcomings of previous research in the field, the aim of the present study was to investigate the cortisol stress response to the TSST and its association with childhood trauma, acute and chronic stress perception and protective factors in a larger group of FEP patients. Based on previous literature, we expected subjective and neurobiological indicators of heightened stress vulnerabiliy to be more pronounced in FEP patients than in healthy controls. In particular, we hypothesized the cortisol response to the TSST to be blunted in patients compared to controls, perceived stress to be elevated, and putative protective factors such as social support, self-esteem and coping skills to be reduced in patients. We furthermore hypothesized that a blunted cortisol response to the TSST in patients would be associated with higher levels of perceived stress, poor protective factors and more severe childhood trauma experiences.

2. Methods

2.1. Participants

A total of 100 subjects participated in the study, 57 of whom were patients diagnosed with a FEP (41 male, 16 female, age 23.9 ± 3.8) and 43 control subjects (23 male, 20 female, age 23.2 ± 3.9). FEP patients were recruited during the two years of their follow-up at the Prevention and Early Intervention Program for Psychosis (PEPP) at the Douglas Mental Health University Institute in Montréal, Canada (Iyer et al., 2015). PEPP offers services over two years for patients between 14 and 35 years of age who experience a first episode of affective or non-affective psychosis. Exclusion criteria for the service were previous treatment with antipsychotic medication for more than 30 days, organic brain damage, pervasive developmental disorder, mental retardation, epilepsy and a forensic history. All FEP subjects were actively enrolled in the PEPP program at the time of the experiment and were deemed clinically stable and fit to participate in the study by the treating psychiatrist and case-manager. Table 1 provides information about diagnoses, symptom severity and medication dose in FEP patients at the time of testing.

The control group consisted of healthy individuals recruited through flyers and advertisements in a local free newspaper in the Montréal area. Absence of any history of mental illnesses and use of psychotropic medication was verified through an interview with the non-patient version of the SCID-I (First et al., 2002b).

In both groups, presence of neuroendocrine disorders or use of steroid based medication generally led to exclusion from the experiment. The study was approved by the McGill University Institutional Ethics Review Board. All volunteers signed a consent form outlining the study procedures before the beginning of the experiment and received monetary reimbursement for their time.

Table 1
Clinical characteristics of first episode psychosis patients.

Diagnosis (N = 57)	
Affective / non-affective psychosis, N (%)	15 (26.3) / 42 (73.7)
Medication (N = 48)	
chlorpromazine equivalent doses (CPZE), M (SD)	240.46 mg (210.03)
Symptom severity, M (SD) (N = 57)	
BPRS total	38.37 (12.56)
Positive symptoms	11.56 (6.31)
Negative symptoms	5.93 (3.21)
Manic symptoms	7.56 (2.62)
Depressive symptoms	7.65 (3.24)
Global assessment of functioning (GAF)	56.09 (20.83)
Duration of untreated illness (DUI), median	256.7 weeks
Duration of untreated psychosis (DUP), median	16.4 weeks
Childhood trauma scores (N = 37)	
CTQ total trauma score	48.35 (17.40)
Physical neglect	8.14 (2.77)
Physical abuse	9.89 (5.24)
Emotional neglect	12.08 (4.49)
Emotional abuse	11.94 (6.23)
Sexual abuse	

Note: CTQ = Childhood trauma questionnaire.

Table 2
Group differences in demographic variables and test statistics.

		Between groups		
	Overall (n = 100)	FEP (n = 57)	Controls (n = 43)	Statistic (df)
Age M (SD)	23.6 (3.8)	23.9 (3.8)	23.2 (3.9)	t (98) = 0.85
Sex, male, n (%)	64 (64.00%)	41 (71.93%)	23 (53.49%)	χ^2 (1) = 3.62
College degree, n (%)	54 (54.00%)	23 (40.35%)	31 (72.09%)	χ^2 (1) = 9.94 **
Relationship status, single, n (%)	86 (86.00%)	52 (91.23%)	34 (79.07%)	χ^2 (1) = 3.00
Ethnicity, caucasian, n (%)	75 (75.00%)	43 (75.44%)	32 (74.42%)	χ^2 (1) = 0.01
Cigarette smoking, > 5/day, n (%)	31 (31.00%)	23 (40.35%)	8 (18.60%)	χ^2 (1) = 5.42 *
Cannabis use, past 3 months, n(%)	35 (35.00%)	27 (47.37%)	8 (18.60%)	χ^2 (1) = 8.91 **

Note: FEP = First episode psychosis.
* Significant at level $p < .05$.
** Significant at level $p < .01$.

2.2. Demographic variables

Demographic variables assessed in both groups were age, gender, education, relationship status and ethnicity. Additionally, participants provided information about smoking habits and illicit drug consumption (Table 2).

2.3. The Trier Social Stress Test

The Trier Social Stress Test (TSST) is a standardized psychosocial stress task consisting of a simulated job interview and a calculation task of 5 min duration each, which have to be performed in front of a committee and a camera (Kirschbaum et al., 1993). Related to space constraints at the clinic, the TSST was slightly modified from the original protocol: the experimenter and confederate were seated behind a one-way mirror and the task had to be performed in front of the mirror and a camera. Auditory contact between committee and participant was secured via an intercom connection. Seeing their own reflection in the one-way mirror has the advantage to promote ego-involvement, which is considered an important factor to increase cortisol levels in psychosocial stress tasks (Mason, 1968). During an anticipation phase, the task was explained, the committee was introduced and the participant was given ten minutes time to prepare for the task. Immediately after the task, the participant received a full debriefing concerning the nature of the task and the goal to increase stress levels. The TSST contains elements of uncontrollability and social-evaluative threat and has been shown to reliably elicit cortisol and other neuroendocrine responses (Dickerson and Kemeny, 2004).

In order to capture the endocrine stress response, salivary cortisol was measured at eight time points before and after the stress task using Salivette® cotton swabs (Sarstedt, Nümbrecht, Germany). Saliva samples were frozen at −20 ° Celsius until analyses and were analyzed with a time-resolved immunoassay with fluorescence detection which has been found to have sufficient reliability and validity (Dressendorfer et al., 1992).

Additionally, in a subgroup of 30 patients and 37 controls, heart rate and blood pressure were measured as indicators of the autonomic or sympatho-adrenal-medullary (SAM) response to stress at the time of saliva sampling, using an automatic blood pressure monitor (Omron IntelliSense HEM-711, Kyoto, Japan).

In order to avoid confounding with the diurnal rhythm of cortisol secretion, the experiment was conducted in the afternoon between 1 pm and 4 pm for all participants. Fig. 1 illustrates the course of the two-hour testing session, which was standardized for all participants.

2.4. Assessment of perceived stress and protective factors

Immediately after completion of the TSST presentation, participants rated their subjective level of stress during the job interview and calculation tasks on a scale from zero to ten. The higher of the two ratings was used for statistical analyses.

Subjective stress perception during the past month was assessed with the perceived stress scale (PSS) (Cohen et al., 1983). The PSS lists 14 feelings and thoughts a person might have when appraising a stressful situation and assesses how frequently these occurred using a five-point scale (never, almost never, sometimes, fairly often, often). The PSS possesses acceptable psychometric properties (Lee, 2012).

Participants' self-esteem was rated with the Self-Esteem Rating Scale (SERS) (Nugent and Thomas, 1993). The SERS is a self-rating scale which assesses various components of self-evaluation with 40 items on a 7-point Likert scale. The questionnaire includes aspects such as self-competence, self-worth, worth concerning others, and social, intellectual and problem-solving abilities. Validation for schizophrenic patients has been conducted by Lecomte et al. (Lecomte et al., 2006).

Social support was rated with the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988), a 12-item Likert-type scale that addresses three sources of social support, namely family, friends and significant others. The scale has been successfully validated for psychiatric in- and out-patients including schizophrenic patients (Cecil et al., 1995; Kazarian and McCabe, 1991).

For measurements of active coping, the Brief COPE (Carver, 1997) was used. The Brief COPE is a short version of the COPE inventory (Carver et al., 1989). It assesses both adaptive and maladaptive, internal and external coping strategies and comprises 14 subscales with two items each in a 4-point Likert response type. Participants were asked to refer to stressful events in general when answering the questions. In the current study, only the Active Coping subscale with the following two items was used: "I concentrate my efforts on doing something about the situation I'm in" and "I take action to try to make the situation better". Good psychometric features of the Brief COPE have been confirmed (Muller and Spitz, 2003).

2.5. Assessment of early life adversity in patients

Early life adversity was assessed with the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998) in a subgroup of patients (N = 37) only. The CTQ is a retrospective self-report inventory with five subscales addressing three types of abuse (physical, emotional, sexual) and two types of neglect (physical, emotional). Each subscale consists of five items and another three items examine extreme response bias. The CTQ possesses good psychometric properties and has been validated for psychiatric populations (Bernstein et al., 1997). Table 1 provides details on childhood trauma ratings in the patient group.

2.6. Clinical and symptomatic assessment in patients

Clinical characteristics assessed in patients were as follows: Duration of untreated illness (DUI) and duration of untreated psychosis (DUP) were assessed with the Circumstances of Onset and Relapse

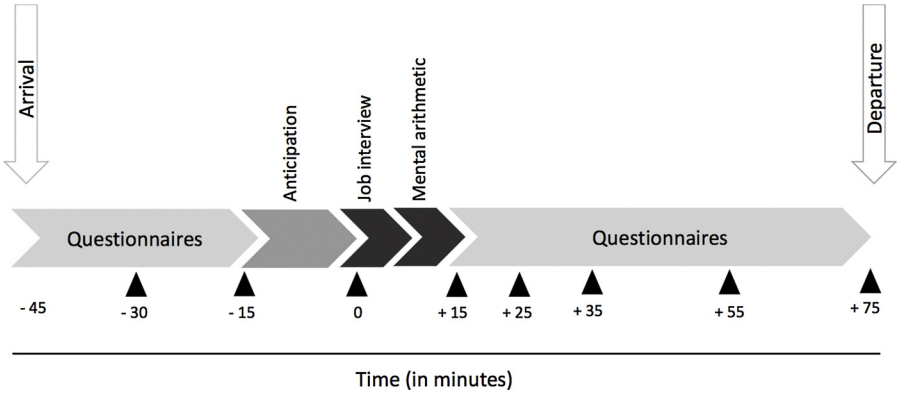

Fig. 1. Physiological assessment times before and after the Trier Social Stress Test (TSST).

Schedule (CORS). The CORS is based on the Interview for Retrospective Assessment of Schizophrenia (IRAOS) (Hafner et al., 1992). A diagnosis of affective or non-affective psychosis was based on the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I) (First et al., 2002a). Positive and negative symptoms of psychosis were rated with the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 2000) at the time of TSST testing, when patients were deemed clinically stable. The BPRS is a semi-structured interview including 24 items that allows medical practitioners to assess schizophrenic symptomatology by means of a 7-point Likert scale. A rating of 1 indicates that the symptom was "not present", and a rating of 7 means that the symptom was "extremely severe". Accordingly, total BPRS scores can range from 24 to 168. A subsequent factor analysis has identified four factors: positive symptoms, negative symptoms, agitation–mania and depression–anxiety. The scale and its four factors have been successfully validated for different illness stages of schizophrenia (Kopelowicz et al., 2008).

General functioning was assessed with the Global Assessment of Functioning (GAF) scale (Luborsky, 1962). As the fifth dimension of diagnostic classification in the DSM (axis V), it assesses psychological, social and occupational functioning. The GAF is a subjective measure rated by clinical psychologists or physicians and ranges from 1 (severe impairment) to 100 (extremely high functioning). Dosage of antipsychotic medication was transferred into chlorpromazine equivalent doses (Woods, 2003). Table 1 shows details of clinical characteristics in the patient group.

2.7. Statistical analyses

Data analysis was performed with the Statistical Package for the Social Sciences 24 (SPSS; IBM, Armonk, NY, USA). Normality of data distribution was tested with Shapiro-Wilk tests. When normality could not be assumed, data were log-transformed. In order to assess differences in demographic and psychological variables between FEP and control subjects, t-tests and χ^2-tests were calculated. Variables showing significant differences between the two groups were utilized as covariates in further analyses.

Group differences in the physiological reactions to the TSST in cortisol were assessed with mixed design ANCOVAs. Time was considered as a repeated within-subjects factor and group (FEP vs. controls) as a between-subjects independent variable. The first assessment time (−30 min) was intended to habituate participants to the experimental situation. Thus, only the remaining seven time points of physiological assessment (−15, 0, +15, +25, +35, +55, and +75 min) were statistically analyzed. In case of violations of sphericity, Greenhouse-Geisser corrections were applied. Additionally, overall cortisol secretion throughout the experimental session was summarized applying the area under the curve with respect to ground (AUCg) and increase (AUCi) (Pruessner et al., 2003). Likewise, AUCg and AUCi were computed for heart rate and systolic blood pressure. While the AUCg refers to the total hormonal output after the challenge task over a certain time period (based on baseline plus change measures), the AUCi reflects only the hormonal change over time (independent of the baseline measures) and thus can be regarded a marker for the sensitivity of the system to stress.

Associations between physiological measures and psychological or symptom variables were calculated using Spearman's rank order correlations. Finally, for patients with information on childhood trauma, the patient group was divided into cortisol responders and non-responders. For better comparability of findings, we followed the procedure suggested by Lange et al. (2017b), who defined AUCi values ≤ 0 as 'non-response' and AUCi values > 0 as 'response'. T-tests were then calculated to assess differences in the severity of traumatic experiences between responders and non-responders.

3. Results

3.1. Group differences in demographic variables

FEP patients and controls did not differ significantly with respect to age, sex, relationship status and visual minority status. Proportionally more control subjects had a college degree as compared to FEP. Tobacco and cannabis use were more frequent in patients than in controls. Table 2 provides information on group differences in demographic variables and smoking habits.

3.2. Group differences in physiological measures

Cortisol levels and heart rate were not normally distributed and were log-transformed for statistical analyses. Additionally, two patients who exhibited cortisol levels more than three standard deviations above the group mean were excluded from these analyses. Fig. 2a–c depicts the results of repeated measures ANOVAs, showing differences in physiological responses to the TSST between FEP patients and controls. Both the FEP and control group showed significant increases in cortisol levels, heart rate and blood pressure in response to the TSST (all $p < .004$), confirming the stressful nature of the task.

With respect to group differences in the endocrine response to stress, overall cortisol levels throughout the TSST were significantly lower in patients compared with controls ($F(1) = 7.38$; $p = .008$). This was also confirmed by a significant group difference in AUCg levels for cortisol ($t(96) = -2.60$; $p = .011$). No group difference was observed for cortisol increase (AUCi) ($p > .65$). The percentage of cortisol non-responders to the TSST was similar in patients and controls (60% vs. 58.1%; $X2(1) = .035$; $p = .508$).

Exploratory analyses revealed that overall heart rate during the TSST was higher in FEP patients compared to healthy controls ($F(1) = 4.72$; $p = .033$). For blood pressure, we observed a significant

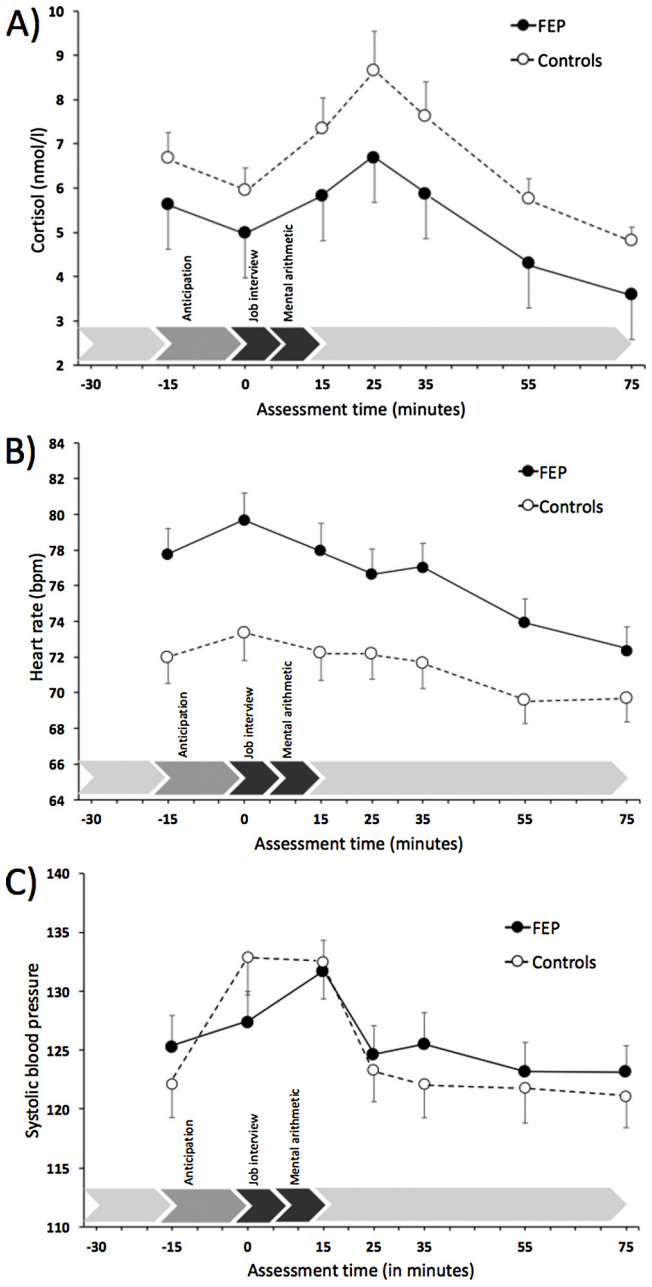

Fig. 2. Group differences in physiological stress markers.

time by interaction effect (F (4.91) = 3.61; p = .004), showing that systolic blood pressure was lower after the anticipation period and elevated for a longer time after the TSST presentation in patients compared to controls. When education, smoking and cannabis use were entered as covariates in the above ANOVAs, the results were still significant (all $p < .04$).

3.3. Group differences in stress and protective factors

FEP and control subjects did not show significant differences in their rating of the stressfulness of the job interview or mental arithmetic task (both p > .77). However, patients showed a trend for higher levels of perceived stress in the past month compared to controls (t (91) = 1.79; p = .077). Furthermore, putative protective factors against stress were lower in FEP in all assessed dimensions. Compared to healthy controls, FEP patients showed significantly decreased levels of self-esteem (M = 25.84 ± 43.82 vs. M = 57.85 ± 32.31; t (94) = -4.12, $p < .001$), perceived social support (M = 4.90 ± 1.30 vs. M = 5.50 ± 1.19; t (92) = -2.30, p = .02), and use of active coping strategies (M = 5.32 vs. M = 5.98; t (92) = -2.27; p = .02).

3.4. Associations among cortisol, heart rate and blood pressure response to the TSST

In healthy controls, a lower cortisol increase during the TSST was correlated with a higher heart rate (rho (35) = −.38; p = .019), but not with blood pressure (p > .22). Heart rate and blood pressure were positively correlated (rho (35) = .39; p = .017). No such association was observed in the patient group (all p > .30). These analyses did not survive Bonferroni correction for multiple comparisons (adjusted α = .05 / 6 = .008).

3.5. Associations between physiological and psychological variables

In the whole sample, decreased general cortisol levels during the TSST (AUCg) were associated with higher levels of perceived stress (rho (89) = −.27; p = .010), less active coping (*rho* (91) = .24, p = .022) and lower self-esteem (*rho* (92) = .29, p = .005). Separating subjects by group revealed that these associations were driven by the patient sample, for whom lower cortisol levels (AUCg) were correlated with reduced self-esteem (*rho* (51) = .29, p = .038) along with trends for increased levels of perceived stress (rho (49) = -.26; p = .062) and active coping (*rho* (50) = .27, p = .054). None of these correlations was significant in the control group (all $p > .39$). No significant associations were observed between cortisol levels and social support (all p > .39). None of the significant correlations would have survived Bonferroni corrections (adjusted α = .05 / 8 = .006). Perceived stress and protective factors were highly inter-related, prohibiting their use as independent factors in regression analyses with cortisol AUCg as dependent variable. Presentation of these correlations is beyond the scope of this study. With respect to the other physiological variables, no significant associations were observed with stress and protective factors in the total group or either subgroup (all p > .34).

3.6. Associations of physiological measures with early life adversity and symptom severity in patients

In the overall patient group, a lower cortisol response was not associated with higher trauma scores (all p > .32), more severe symptoms or lower global functioning (all p > .14). However, when separating the patient group into responders and non-responders to the TSST, patients who did not show a cortisol response to the TSST reported significantly higher levels of physical neglect during childhood (t (32.9) = 2.44; p = .020; Table 3). This result was not significant anymore when adjusting α according to the number of CTQ subscales (.05 / 5 = .01). No differences between responders and non-responders were observed in the other CTQ subscales or any symptom measures (all p > .20).

3.7. Medication effects on physiological, psychological and clinical variables

Chlorpromazine equivalent doses of medication at the time of TSST testing were available for 46 patients. Exploratory analyses on CPZE doses did not show relations to the patients' cortisol levels (p > .58). However, higher medication doses were associated with more severe positive symptoms at trend level (rho = .27; p = .067) and with significantly better active coping strategies (rho (41) = .33; p = .030). No further associations between medication dose and symptom or psychological variables were observed (all p > .10).

Table 3
Difference in childhood trauma scores in cortisol responders and non-responders.

CTQ subscale	Non-responders (N = 21)	Responders (N = 15)	Statistic *(df)*
Physical neglect, mean (SD)	9.048 (3.06)	7.067 (1.79)	t (33) = 2.440*
Physical abuse, mean (SD)	9.857 (5.03)	9.933 (5.87)	t (34) = -0.042
Emotional neglect, mean (SD)	12.762 (4.44)	11.600 (4.39)	t (34) = 0.778
Emotional abuse, mean (SD)	11.857 (6.32)	12.533 (6.24)	t (34) = -0.318
Sexual abuse, mean (SD)	6.428 (3.76)	6.333 (3.31)	t (34) = 0.079

Note: CTQ: Childhood Trauma Questionnaire; Non-responders: no cortisol increase following the Trier Social Stress Test (TSST); Responders: Cortisol increase following the TSST.
* Group differences significant at $p < .05$.

4. Discussion

The present study shows an intact cortisol *response* to the TSST in psychosis patients that was comparable to controls, but significantly lower cortisol levels throughout the two-hour afternoon testing period in patients. Subjective ratings of perceived stress tended to be elevated whereas putative protective factors towards stress, such as self-esteem, social support and coping skills, were reduced in patients. Lower cortisol levels were associated with higher levels of perceived stress, poor protective factors and more physical neglect during childhood predominantly in patients.

Our results add to the growing body of literature investigating the cortisol response to an acute challenge task in psychosis. However, the observation of an intact cortisol response to a psychosocial stress test is surprising as it does not correspond with the majority of reviews concluding that the cortisol response in patients is blunted compared to healthy controls (Borges et al., 2013; Ciufolini et al., 2014; Pruessner et al., 2017; Zorn et al., 2017). In our own previous studies in individuals at clinical high risk, we observed a reduced cortisol slope over the initial 10 min after the psychosocial stress task, which was discussed as an indication for a blunted cortisol response in patients (Pruessner et al., 2013a). However, in line with the present findings, cortisol increase assessed with the AUCi was not different, and cortisol levels throughout the afternoon testing period were blunted in high risk compared to control subjects (Pruessner et al., 2013a).

A recent review has noted that the number of studies investigating the cortisol stress response in schizophrenia is limited and show evidence for a publication bias (Zorn et al., 2017). Indeed, another recent review including studies with larger and more chronic patient groups as well as other psychosocial stress task could not confirm a blunted cortisol response in patients (Lange et al., 2017a). It is thus possible that our finding of an intact cortisol response to the TSST can be explained by the larger and more heterogeneous patient group, including both affective and non-affective psychosis. Inconsistent results might also be due to differences in the timing of the stress test. Previous studies have shown that the time of day when the TSST is conducted plays a role in the responsiveness of the HPA axis (Kudielka et al., 2004; Maheu et al., 2005). In the present study and our previous report in high risk individuals, the TSST was conducted at the same time in the afternoon for all study participants, allowing sufficient room for a cortisol response, at a time of relatively low baseline cortisol levels.

Our finding of generally lower cortisol levels in patients compared to controls contradict previous reports of elevated baseline cortisol levels in patients with psychosis (Borges et al., 2013; Pruessner et al., 2017). It is possible that antipsychotic medication contributed to these reduced baseline cortisol levels (Hempel et al., 2010; Houtepen et al., 2015). Since a blunted cortisol response to psychosocial stress has been found in unmedicated FEP patients (van Venrooij et al., 2012) and in our previous study with medication naïve persons at elevated risk for psychosis (Pruessner et al., 2013a), antipsychotic medication may have helped to normalize the cortisol response to acute stress. Indeed, most of the FEP patients in the current study were receiving antipsychotics. However, the dosage of antipsychotic medication was not related to cortisol levels during the TSST, and exploratory analyses in the four unmedicated versus all medicated patients, did not reveal a difference in cortisol levels ($p > .60$; data not shown).

The finding of reduced cortisol levels in psychosis patients support previous reports of hypocortisolism in association with post-traumatic stress disorder and many other stress related disorders (Heim et al., 2000). A flattened diurnal rhythm of cortisol has also been noted in relation to high levels of psychosocial risk factors, including depression and vital exhaustion (Sjogren et al., 2006). Here, it has been discussed that a state of chronic stress and longstanding HPA axis activation can cause adrenocortical insufficiency, evident in reduced cortisol secretion (Fries et al., 2005; Heim et al., 2000). A flattened circadian rhythm of cortisol secretion might also be expected following a blunted cortisol awakening response (Pruessner et al., 2013b).

Another reason for the generally lower cortisol levels in the current study could have been that FEP patients showed diminished engagement with the task compared to controls, possibly related to lower education level, reduced self-esteem and coping skills or due to cannabis use. However, both groups appraised the TSST as similarly stressful and showed increases in measures of endocrine and autonomic function, attesting to the perception of the task as stressful.

Interestingly, in our previous study in medication naïve individuals at elevated risk for psychosis, we observed an attenuated cortisol response, but heart rate and blood pressure were also reduced (Pruessner et al., 2013a). The elevated autonomic response seen in the present study could be an effect of medication (Marano et al., 2011) or an indicator of higher stress or anxiety levels (Michail and Birchwood, 2014) in FEP patients compared to controls. These elevated autonomic markers might have interacted with the activation of the HPA axis, which in turn could have contributed to the observed lower cortisol response. Such compensatory functions of SAM and HPA axis have been previously described in healthy controls (Andrews et al., 2012; Andrews and Pruessner, 2013).

Given these finding of generally blunted cortisol levels, it is possible, that a cortisol response to the mental challenge task was indeed present in previous studies, but was masked by lower background cortisol levels. It is unclear to what extent previous studies in psychosis have attempted to make a distinction between background cortisol levels, on which the acute reaction is superimposed (AUCg), and the reactivity itself (AUCi) when investigating cortisol levels during the TSST. Certainly, a better understanding of the relationship between basal and reactive HPA axis measures in psychosis would help to explain inconsistent results and could inform current models of HPA axis function in psychosis (Pruessner et al., 2017; Shah and Malla, 2015).

Whereas acute stress perception during the TSST was similar in patients and controls, perceived stress during the past month tended to be higher and self-esteem, social support and active coping skills were rated significantly lower by patients than controls. A lack of these putative protective factors is likely to reflect poor resilience towards stress (Mizuno et al., 2016; Tait et al., 2004). Higher levels of perceived stress, lower self-esteem and coping skills were furthermore related to attenuated cortisol levels in the patient group. These findings support the neural diathesis-stress model of schizophrenia proposing that patients

show increased stress vulnerability mediated by altered HPA axis regulation (Pruessner et al., 2017; Walker and Diforio, 1997).

Interestingly, in the present study, we found a relatively high number of cortisol non-responders to the TSST. A previous study defining responders and non-responders in the same way had observed a slightly lower rate of non-responders (52% as opposed to 58% in the current study) in first episode psychosis patients (Lange et al., 2017b). It is possible that the modified set-up of the TSST in the current study, foremost the fact that participants faced a one-way mirror during their presentation instead of looking at the committee directly, contributed to the larger number of non-responders. Nonetheless, the participants faced their own reflection in the mirror which, due to the induction of ego-involvement (Mason, 1968), arguably could have been equally stressful than facing the committee. It should be noted that considering the diurnal decline in cortisol levels, the method applied here to separate responders and non-responders by cortisol 'increase' versus 'no increase' has likely over-estimated the number of non-responders. However, the difference in cortisol levels between groups cannot be attributed to a larger number of cortisol non-responders among patients. In fact, the percentage of non-responders was similarly high (about 60%) in both the patient and control group.

The finding that cortisol non-responders to the TSST reported higher levels of physical neglect during childhood contradicts the recent observation by Lange et al. (Lange et al., 2017b) that a history of trauma in psychosis patients was only present in responders to the TSST. Whereas the higher cortisol response in the Lange et al. study was associated with emotional abuse, the lower response in the present study was related to physical neglect. Neither of the two studies found differences in any other type of childhood trauma. While physical neglect has been associated with a more severe psychopathological profile in some studies (Garcia et al., 2016; Schalinski et al., 2015), physical abuse and emotional neglect and abuse might be even more relevant types of adversity (Fisher et al., 2010; Garcia et al., 2016; Pruessner et al., 2018; Schalinski et al., 2015).

Presenting the first study to investigate the association between childhood trauma and the cortisol response to the TSST in psychosis, the authors were careful with the interpretation of their finding and argued that both hypo- and hyper-responsiveness to psychosocial challenge tasks could reflect traumatic experiences (Lange et al., 2017b). In contrast, the observations of the present study resemble previous findings in healthy controls, showing that people who had experienced childhood adversity exhibit reduced cortisol levels in response to psychosocial stress (Bunea et al., 2017).

Attempting to explain the contradictory findings in the association between childhood trauma and cortisol levels between the Lange et al. and the present study, it should be kept in mind that in both studies, the results would not have survived statistical adjustment for multiple comparisons. As a consequence, findings from both studies have to be considered preliminary and interpreted with caution.

In addition, a number of methodological differences between the two studies could have contributed to the contradictory results on childhood trauma and cortisol response. While the proportion of men and women, the timing of the TSST, and the definition of cortisol responders and non-responders were comparable between the two studies, the present study included a larger group of patients, patients were diagnosed with a first episode of psychosis as compared to chronic illness and were thus younger and had a shorter duration of illness. Other potentially relevant differences concerned the TSST modifications. While the Lange et al. renounced the recording equipment and had participants talk about their physical appearance, in our study, the committee was seated behind a one-way mirror but the presentation included a job interview. Future studies will have to confirm our finding of higher trauma ratings in relation to a reduced cortisol stress response. Together with our observation of reduced cortisol levels in association with higher levels of perceived stress and diminished protective factors in patients, such confirmation could be regarded as support for the notion of heightened sensitivity to subsequent stress following early life adversity (van Winkel et al., 2008; Veling et al., 2016), evident in higher subjective stress responses (Rauschenberg et al., 2017; van Nierop et al., 2018; Veling et al., 2016) and altered HPA axis regulation (Champagne, 2013; Liu et al., 1997; van Winkel et al., 2013).

Alterations in HPA axis function are just one pathway in the complex interplay among psychological and biological factors affecting psychosis onset and progression (Pruessner et al., 2017). The long-term effects of childhood trauma are believed to affect stress vulnerability mediated by epigenetic and other processes causing alterations in autonomic, endocrine and immune systems (Anisman et al., 1998; Heim and Binder, 2012; Liu et al., 1997). Importantly, the experience of childhood trauma does not only seem to have implications for psychosis onset, but also for clinical outcome over time (Pruessner et al., 2018; Trotta et al., 2015).

The present study has both strengths and limitations. It can be considered a strength, that the current study included a larger number of patients than previous reports, restricted the clinical group to first episode psychosis patients and applied the Trier Social Stress Test, which has been proven to be a powerful method to induce stress. However, the high number of cortisol non-responders, possibly attributable to the modified version of the TSST, could be considered a limitation. Other limitations are the smaller number of participants for whom autonomic measures were available and that childhood trauma ratings were only available in patients and for a subgroup of patients. Additionally, CPZE medication dose could not be calculated for all medications and was thus only available for a subgroup of patients. Finally, the number of female and un-medicated patients ideally would have been higher to allow for meaningful statistical analyses in these subgroups.

In summary, the results of the present study show generally reduced cortisol levels in the afternoon and sustained reactivity of the HPA axis in first episode psychosis patients during the Trier Social Stress Test. Lower cortisol levels were associated with higher self-reported stress, diminished protective factors towards stress and higher levels of physical neglect during childhood. The findings support the assumptions of the neural diathesis-stress model of schizophrenia, proposing that the interplay between vulnerability factors and stressful experiences, particularly in early life, affects the propensity towards psychosis formation and exacerbation, mediated by alterations in HPA axis functioning. The observed relationship of cortisol levels during the TSST with psychological indicators of stress and resilience in patients support the notion that attenuated cortisol levels are a marker of increased stress vulnerability in psychosis.

An important next step would be to translate the accumulating research knowledge on dysregulation of the HPA axis into clinical applications (Hellhammer et al., 2018). Here, it will be important to consider the multiple variables related to stress vulnerability, that have been identified as risk factors for psychosis onset and progression (Pruessner et al., 2017), and to find ways to include these variables and their modifiers into elaborate research designs as well as routine clinical assessments, so that the knowledge bases gathered on both sides can complement and fertilize each other.

Declarations of interest

None.

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