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Hair cortisol concentrations as an indicator of potential HPA axis hyperactivation in risk for psychosis

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ABSTRACT

A chronic hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis is assumed to be an important indicator of vulnerability for psychosis. Despite the considerable research on this topic, putative social origins of HPA axis hyperactivation have received little attention in the literature so far. Also, the inconsistency of previous findings calls for new and reliable methods in the assessment of HPA axis activation. To address these issues, we used hair cortisol concentrations as an indicator of chronic HPA axis activation in participants at elevated risk for psychosis (clinical risk: $n = 43$, familial risk: $n = 32$) and low-risk controls ($n = 35$), and assessed its relation with a variety of social stressors. We also tested the interaction effect between social stressors and familial risk status on hair cortisol concentrations (moderation analysis). Participants at elevated risk for psychosis did not show significantly higher hair cortisol concentrations than low-risk controls. However, severe social stressors (child abuse experiences, traumatic events) predicted hair cortisol concentrations in the total sample. This relationship was not significantly moderated by familial risk status (as a marker of genetic risk). The results challenge the assumption that HPA axis hyperactivation is an early vulnerability indicator for psychosis but leave the possibility that it manifests only at more severe risk stages. Furthermore, the findings suggest that acquired experiences contribute to the emergence of HPA axis hyperactivation, which might occur via a gene-environment correlation rather than via a gene-environment interaction.

1. Introduction

It is generally agreed that stress plays a pivotal role in the etiology of psychosis (e.g., Lincoln et al., 2015; van Winkel et al., 2008; Walker et al., 2008). Nevertheless, questions remain about the processes that mediate the association between stress exposure and the exacerbation of psychotic symptoms. Relating to this question, the hypothalamic-pituitary-adrenal (HPA) axis, as one of the major physiological stress response systems, has been the focus of interest in the recent decades and a potential hyperactivity of this system has been suggested to constitute an important vulnerability indicator in psychosis (Walker et al., 2008; Walker and Diforio, 1997). Increasing empirical evidence confirms a chronic HPA axis hyperactivation in patients with psychotic disorders (Pruessner et al., 2017). However, it remains to be examined whether HPA axis hyperactivation is also present in people at risk for psychosis. Moreover, further research is needed to elucidate its origins.

In order to ascertain that HPA axis hyperactivation is, indeed, a vulnerability indicator for psychosis, it would be helpful to show that it is not only present in patients with manifest psychosis but also in groups at elevated risk for psychosis. Risk states for developing psychosis are commonly defined by several characteristics (Keshavan et al., 2011): One is the presence of psychotic-like experiences which has been termed *clinical risk* (Linscott and van Os, 2013). Another is a familial relationship to an affected person, commonly referred to as genetic or *familial risk* (e.g., Sullivan et al., 2003; Tandon et al., 2008). Characteristic indicators of chronic HPA axis hyperactivation are elevated hormonal levels (e.g., cortisol; single baseline levels or repeatedly measured diurnal levels) or structural changes in the brain (e.g., pituitary gland enlargement or hippocampus volume reduction). In clinical as well as familial risk groups, studies have found elevated baseline cortisol levels (e.g., Carol and Mittal, 2015; Collip et al., 2011; Walker et al., 2013; Yildirim et al., 2011), smaller hippocampal volumes (e.g., Wood et al., 2010; van Erp et al., 2004), and larger pituitary glands (e.g., Mondelli et al., 2008; Takahashi et al., 2013) in comparison to control groups. However, although these studies point to a chronic HPA axis hyperactivation in at-risk groups for psychosis, there are also conflicting results that show no differences between at-risk groups and controls (e.g., Day et al., 2014; Shah et al., 2015) or even indicate hypoactivation (smaller pituitary volumes in male subjects of an at-risk group; Romo-Nava et al., 2013).

The inconsistencies of findings related to chronic HPA axis activation in both clinical and familial at-risk samples (Pruessner

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et al., 2017) might stem from methodological disadvantages of the traditional HPA axis assessment methods. Some are susceptible to situational influences (i.e., baseline cortisol levels) others constitute rather indirect measures of long-term hormone secretion (i.e., structural indicators). A comparatively new indicator of chronic HPA axis activation, the cortisol incorporated into scalp hair, might overcome some of these disadvantages as it allows investigating cortisol secretion retrospectively over a period of several months. In the past decade, evidence on the methods' validity (e.g., Kirschbaum et al., 2009; Thomson et al., 2010; Short et al., 2016) and reliability (Short et al., 2016; Stalder et al., 2012) has accumulated, rendering it a promising measure of longer-term cumulative cortisol secretion that indicates chronic HPA axis activation.

Furthermore, questions arise about the origins of HPA axis hyperactivation. Most commonly, HPA axis activation is considered to be determined by stressors (e.g., Chrousos, 2009). Manifold evidence shows that social stressors, such as child abuse, migration, bullying and low socioeconomic status are associated with an elevated psychosis risk status (e.g., Fusar-Poli et al., 2017; Jaya and Lincoln, 2016). Independent of psychosis, these types of stressors have also been found to be associated with elevated cortisol levels (e.g., González-Cabrera et al., 2017; Jackson et al., 2016; Squires et al., 2012). Moreover, there is preliminary evidence for a link between social stressors and cortisol levels in psychosis (Read et al., 2014) and in at-risk samples (Cullen et al., 2015, 2014; Labad et al., 2015; Thompson et al., 2007). However, most studies on HPA axis activation in people at risk for psychosis either did not assess past social stressors at all, or else assessed a very limited number of social stressors. Thus, more evidence is needed on the relationship between a broad range of social stressors and chronic HPA axis activation in people at risk for psychosis.

Findings on HPA axis hyperactivation in familial risk for psychosis suggest that genetic factors also contribute to this vulnerability indicator. This view is supported by tentative evidence indicating that certain genetic polymorphisms involved in HPA axis activation are associated with psychosis (Schatzberg et al., 2014; Steen et al., 2010). Hence, both genetic and social factors seem to influence HPA axis hyperactivation. In line with a vulnerability-stress concept, it is intuitive to assume that a combination of genetic and social influences explains an even larger impact on HPA axis hyperactivation than either factor alone. This assumption is substantiated by studies showing the effect of stress exposure on HPA axis activation to be stronger in individuals with a genetic risk for psychosis compared to controls (Aas et al., 2013, 2014; Collip et al., 2011; Cullen et al., 2015). However, there are only few studies on this topic and these have focused mainly on the impact of childhood adversities.

To corroborate and extend previous research that found chronic HPA axis hyperactivation in people at risk for psychosis we used hair cortisol concentrations as a novel methodology. We compared hair cortisol concentrations in clinical and familial risk groups with those in low-risk controls and assessed the extent of previous exposure to a broad range of social stressors, including child abuse experiences, trauma, migration, bullying, ostracism, minority group affiliation, discrimination, socio-economic deprivation and social undermining. We expected (1) participants at clinical and familial risk for psychosis to show elevated hair cortisol concentrations compared to a low-risk control group. Furthermore, we hypothesized that (2) social stressors would predict hair cortisol concentrations and that (3) familial risk status would moderate this association. Specifically, we expected that participants at familial risk for psychosis would show a stronger association between social stressors and hair cortisol concentrations than low-risk control participants.

2. Methods

2.1. Participants

We estimated the required sample size for a one-way ANOVA with two groups and a multiple regression analysis with G*Power 3.1.9.2 (Faul et al., 2009). The calculation was conducted for a power of 0.90, $\alpha = 0.05$, and a medium to large effect size ($f = 0.35$). It yielded a minimum sample size of $n = 88$ for the one-way ANOVA, which is also sufficient for the planned multiple regression analyses.

Three different groups were recruited for the study, a familial risk group (FR, $n = 32$), a clinical risk group (CR, $n = 43$) and a low-risk control group (LR, $n = 35$) resulting in a total sample of $N = 110$. Participants were recruited via notices in public buildings and in online portals. For FR, additional announcements were made in support groups for family members of patients with mental disorders. All participants were requested to have a minimum hair length of 3 cm, to be aged between 18 and 65 years, and to have a good command of the German language. Reasons for exclusion were lifetime diagnosis of a psychotic, neurological or endocrine disorder, pregnancy, a body mass index >35, or taking glucocorticoids and antipsychotics. The additional exclusion of participants with a coronary heart disease or cardiac medication (e.g., ACE-inhibitors) was necessary due to the assessment of cardiac parameters in a second part of the study, which will be reported elsewhere. FR were required to have at least one first-degree relative (parent, sibling or child) diagnosed with a psychotic disorder. CR were selected to have subclinical psychotic-like experiences, i.e., a score of $\geq$9.0 on the positive symptoms subscale of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). Thus, CR scored higher than 50% of the participants in a large German community sample ($Med = 8.0$; Schlier et al., 2015). LR had to score < 9.0 on the positive symptom subscale of the CAPE, had to have no first-degree relative diagnosed with a psychotic disorder, and to not fulfill criteria for any mental disorder.

2.2. Procedure

The study was approved by the Faculty Ethics Committee at the Universität Hamburg. All participants provided informed consent prior to participation. CR completed an online prescreening for subclinical psychotic experiences by means of the CAPE (Stefanis et al., 2002), and all participants underwent a group-specific eligibility check by telephone. If eligible, they partook in a subsequent face-to-face interview: In FR and CR, clinical symptoms were assessed by the Structured Clinical Interview for DSM-IV, axis I (SCID-I; Wittchen et al., 1997). In LR, Axis-I disorders were ruled out by the SCID-I. Furthermore, all participants answered to an online battery of self-report measures (see below). Finally, hair strands with a diameter of at least 3 mm were cut with fine scissors next to the scalp at the posterior vertex. The hair strands were enveloped in aluminum foil, labeled for identification of the segment nearest to the scalp and stored in a dry room.

2.3. Self-report measures

The lifetime frequency of psychotic-like experiences was assessed by the CAPE (Stefanis et al., 2002), which includes questions about positive symptoms (20 items), negative symptoms (14 items) and depressive symptoms (8 items). Discriminant and convergent validity as well as test-retest reliability have been approved (Konings et al., 2006). We used the frequency subscale of the German version validated by Schlier et al. (2015), for which each item is answered on 4-point Likert scales between *never* and *almost always*.

To assess different relevant aspects of social stress exposure, we used a comprehensive battery of measures:

(1) The Multidimensional Socioeconomic Status Index (Lampert and Kroll, 2009) was used to measure the socioeconomic status. Scores for educational level, type of current job (e.g., self-employed, public servant) and income level each ranged between 1 and 7. The three values were summed up to range between 3 (lowest socioeconomic status) and 21 (highest socioeconomic status);
(2) Migration status was assessed following Schenk et al. (2006). For a multilevel score, a value of 1 was assigned if both parents were not born in Germany or if the participant's first language was not German, a value of 2 if the participant and at least one parent was not born in Germany, (total score: 0–2);
(3) A measure from the NEMESIS study (Janssen et al., 2003) was used to define the minority status. It contains five dichotomous items on physical disability, sexual orientation, ethnic group, religious group, and physical appearance (total score: 0–5);
(4) Perceived discrimination was also assessed by a measure from the NEMESIS study (Janssen et al., 2003). Seven dichotomous items were used to assess the experience of discrimination (age, gender, and the minority status categories; total score: 0–7);
(5) The Social Undermining Scale (Vinokur and van Ryn, 1993) measures the frequency of negative social interactions. Five items are answered on 5-point Likert scales (range 1–5) between *not at all* and *a great deal*. The scale has good internal consistency (Cronbach's $\alpha = 0.89–0.92$) and correlates negatively with social support (Vinokur and van Ryn, 1993). All items were summed and averaged;
(6) The Ostracism Experience Scale (Carter-Sowell, 2010) consists of eight items to be rated on 7-point Likert scales between *hardly ever* (1) and *almost always* (7). The scale's internal consistency is excellent ($\alpha = 0.94$; e.g., Hales et al., 2016) and Carter-Sowell (2010) report evidence for convergent and discriminant validity. We calculated the mean score of all items;
(7) The Bullying Victimization Questionnaire (Wolke and Sapouna, 2008) was employed to measure bullying victimization at home, at school and at work. Six items are rated on 5-point Likert scales between *never* (1) and *several times per week* (5). All items were summed and averaged;
(8) Child abuse experiences were measured by four questions on emotional, psychological, physical, and sexual abuse. They are derived from a semi-structured interview (Janssen et al., 2004) and answers have to be provided on 6-point Likert scales between *never* (0) and *very often* (5). We calculated the mean score of all items;
(9) The Trauma History Questionnaire (Green, 1996) assesses self-reported exposure to crime-related events, accidents, natural or other disasters, sexual and physical violence. It consists of 24 dichotomous items (total score: 0–24) and shows good reliability and validity (see Hooper et al., 2011).

2.4. Hair cortisol analysis

The hair cortisol analysis was conducted by the Dresden Lab-Service GmbH (Prof. Dr. Clemens Kirschbaum laboratory in Dresden, Germany). Only the 3 cm nearest to the scalp were included in the analysis. Since hair grows at a rate of approximately 1 cm per month, a length of 3 cm should reflect cortisol secretion of the last three months. Immunoassays with chemiluminescence detection were used to ascertain cortisol concentrations. The intraassay and interassay coefficient of variance of this assay is below 8%. For further details of the procedure see Kirschbaum et al. (2009).

2.5. Statistical analyses

The analyses were conducted using IBM SPSS (version 24; IBM Corp., Armonk, NY). Group differences between the risk groups (FR and CR) and LR in hair cortisol concentrations were tested by univariate ANOVAs (hypothesis 1). In order to test whether the social stress measures were associated with hair cortisol concentrations, we first correlated all social stress measures individually with these and used Bonferroni corrected significance levels. Stressors that were significantly correlated with hair cortisol concentrations were then entered in a multiple linear regression analysis in the total sample (hypothesis 2). In order to test whether the association between the social stressors and hair cortisol concentrations would be stronger in familial risk than in low-risk status (hypothesis 3), we used the PROCESS macro 3.0 (Hayes, 2018). We conducted the moderation analyses defining each of the social stressors, separately, as the respective predictor, familial risk status (FR versus LR) as the moderator, and hair cortisol concentrations as dependent variable. A moderation effect would be indicated by a significant interaction term of familial risk status × the respective social stressor (bootstrapping was based on 5000 samples; due to violation of homoscedasticity assumption, we used heteroscedasticity consistent confidence intervals, Davidson and MacKinnon, 1993).

One participant was taking glucocorticoid medication (daily intake of Fluticasonfuroat), which had not been mentioned in the telephone interview prior to participation but had been noted in the laboratory assessment. As glucocorticoid medication was an exclusion criterion we excluded this case from the hair cortisol analyses, resulting in a sample of $N = 109$.

Since the study groups differed in BMI and age (see Table 1), we tested whether these two variables were significant covariates in the group comparison of hair cortisol. As this was not the case, we did not include these two variables in the final analyses. As age correlated with socio economic status and number of traumatic events, we added age as a covariate in the respective analyses. Due to a technical problem, two questionnaires contained some missing values (Trauma History Questionnaire: 12 item values, i.e., 0.45% of the total item values, CAPE: 7 item values, i.e., 0.32% of the item values). Since the percentage of missing values was very small and the gold standard method for substituting missing data (multiple imputation) cannot be used with the PROCESS macro in SPSS, we substituted the missing

Table 1
Demographic characteristics in the clinical risk group, in the familial risk group and in low-risk controls.

Variable		CR (n=43)	FR (n=32)	LR (n=35)	Test statistics	
Age	*M* (*SD*)	26.2 (8.2)	33.3 (12.4)	27.3 (9.6)	F=5.13, p=.01	FR > CR
Gender	% male/female/other	32.6/65.1/2.3	31.3/65.6/3.1	37.1/62.9/0.0	$\chi^2(4)$=1.22, p=.88	–
Education	*M* (*SD*)	5.6 (0.9)	5.4 (1.3)	5.5 (1.1)	F=0.13, p=.88	–
CAPE positive subscale	*M* (*SD*)	14.8 (5.7)	5.8 (4.0)	3.6 (2.1)	F=74.04, p<.001	CR > FR > LR
BMI	*M* (*SD*)	22.6 (3.3)	24.0 (3.2)	21.8 (2.8)	F=4.30, p=.02	FR > LR
Smoking	% yes/no	14.6/85.4	25.0/75.0	17.1/82.9	$\chi^2(2)$=1.34, p=.51	–

Note. Educational level ranged from 1 (no school leaving qualification) to 6 (qualification for university entrance), CR= clinical risk group; FR=familial risk group LR=low-risk controls, CAPE=Community Assessment of Psychic Experiences; BMI=body mass index.

Table 2
Differences between the risk groups and low-risk controls in the social stress measures.

Variable	CR	FR	LR	CR vs. LR		FR vs. LR	
	M (SD)	*M (SD)*	*M (SD)*	*F*	$\eta^2_{partial}$	*F*	$\eta^2_{partial}$
Socioeconomic status (3-21)	9.1 (2.9)	11.3 (4.2)	10.6 (3.8)	3.54	0.05	0.42	0.01
Migration (0-2)	0.5 (0.8)	0.3 (0.7)	0.2 (0.6)	3.18	0.04	0.84	0.01
Minority Status (0-5)	0.5 (0.8)	0.3 (0.5)	0.2 (0.4)	4.02	0.05	1.52	0.02
Perceived Discrimination (0-7)	1.4 (1.3)	1.2 (1.4)	0.3 (0.5)	20.32***	0.21	11.94*	0.16
Social Undermining (1-5)	1.6 (0.7)	1.6 (0.6)	1.4 (0.5)	1.73	0.02	1.09	0.02
Ostracism Experience (1-7)	1.6 (0.8)	1.4 (0.6)	1.2 (0.5)	5.45	0.07	1.77	0.03
Bullying Victimization (1-5)	2.0 (0.7)	2.1 (0.8)	1.4 (0.5)	18.15**	0.19	18.00**	0.22
Child Abuse (0-5)	0.8 (1.0)	1.1 (1.0)	0.1 (0.4)	14.38**	0.16	27.73***	0.30
Trauma (0-24)	3.2 (2.4)	5.0 (3.4)	2.8 (2.9)	1.16	0.02	5.37	0.08

Note. Group differences are Bonferroni corrected. For socioeconomic status and trauma age is entered as a covariate; CR= clinical risk group; FR=familial risk group; LR=low-risk controls.
* $p<.05$
** $p<.01$
*** $p<.001$

values by the mean of the participants' remaining item values. We double checked whether any of the other analyses produced different findings when using multiple imputation, which was not the case.

3. Results

3.1. Descriptive statistics and preliminary analyses

Demographic characteristics of the samples are displayed in Table 1. In the CR sample, 13 participants currently met criteria for one or more than one mental disorder (depressive disorders: $n = 6$, bipolar disorders: $n = 2$; social phobia: $n = 2$, hypochondria: $n = 1$, specific phobias: $n = 4$; bulimia nervosa: $n = 1$). Among the FR sample, seven participants met criteria for a mental disorder (depressive disorders: $n = 5$; specific phobias: $n = 2$, bipolar disorders: $n = 1$). Table 2 shows the occurrence of social stressors in the three study groups. Bonferroni corrected group differences showed that both risk groups reported more perceived discrimination, more bullying victimization and more child abuse experiences.

3.2. Hypotheses testing

Concerning hypothesis 1, hair cortisol concentrations were not significantly different between the at-risk participants (CR and FR) and the low-risk control group, $F(1,107) = 2.39$, $p = .13$, $\eta^2_{partial} = 0.02$. Similarly, no risk group differed significantly from the low-risk controls in the subsequent subgroup analyses, CR: $F(1,75) = 1.70$, $p = .39$, $\eta^2_{partial} = 0.02$, FR: $F(1,65) = 2.21$, $p = .28$, $\eta^2_{partial} = 0.03$. Group means of the hair cortisol concentrations are displayed in Fig. 1.

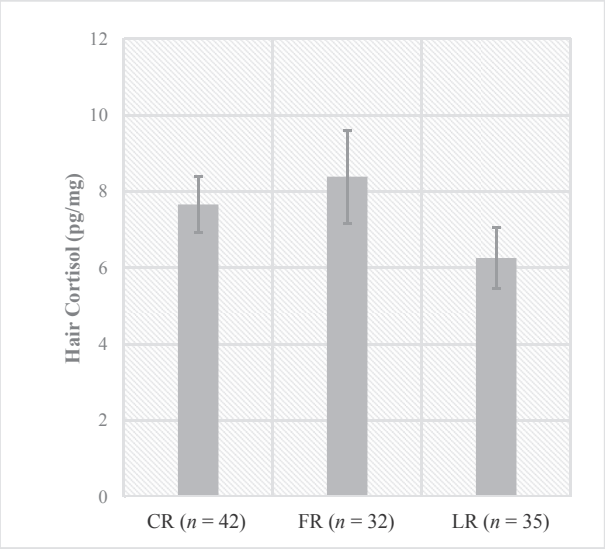

Fig. 1. Group means (and standard error of the mean) for hair cortisol concentrations.

In line with hypothesis 2, hair cortisol concentrations were significantly associated with traumatic events ($r = 0.32$, $p = .01$) and with child abuse experiences ($r = 0.28$, $p = .03$; see Table 3). A multiple regression model with these two social stress measures as predictors of hair cortisol concentrations (and age as a covariate) was significant, $F(3,105) = 4.90$, $p = .003$, $R^2 = 0.12$. More traumatic events significantly predicted higher hair cortisol concentrations, $b = 0.46$, $SE = 0.20$, $p = .02$, whereas child abuse experiences was rendered a non-significant predictor in this model, $b = 0.88$, $SE = 0.60$, $p = .14$.

In regard to hypothesis 3, we found no significant interaction term of familial risk status × social stressor (see Table 4).

3.3. Supplementary analyses

We inspected the data of each group for outliers based on the interquartile range (IQR), which comprises the second (Q_2) and third quartile (Q_3) of the data: Values > $Q_3 + 3$*IQR or < $Q_2 - 3$*IQR were defined as outliers. According to this definition, the data showed one outlier for LR (22.39 pg/mg). Excluding this value from the analysis changed the results insofar, as the at-risk participants showed higher hair cortisol concentrations compared to the low-

Table 3
Single correlations between the social stress measures and hair cortisol concentrations in the total sample.

Social stress measure	Hair cortisol concentrations
	r
Socioeconomic status	0.08
Migration	0.10
Minority status	0.10
Perceived discrimination	0.05
Social undermining	0.02
Ostracism experience	-0.04
Bullying victimization	0.07
Child abuse	0.28*
Trauma	0.32*

Note. N=109; Pearson's correlation (partial correlation for trauma and socioeconomic status controlling for age); the significance level of the correlations is Bonferroni corrected.
* $p < .05$.

Table 4
Coefficients of the moderation analyses with familial risk (FR) status as a moderator of the association between social stressors and hair cortisol concentrations.

Variable	*B*	*BCa CI* [LLCI, ULCI]	*SE*	*t*	*p*	R^2
Socioeconomic status	-0.1	[-0.8, 0.6]	0.3	-0.3	.79	.15
FR status	2.1	[-1.2, 5.5]	1.7	1.3	.21	
Socioeconomic status × FR status	0.8	[-0.3, 1.9]	0.5	1.5	.13	
Migration	0.5	[-1.4 , 2.4]	1.0	0.5	.60	.04
FR status	2.0	[-0.9, 5.0]	1.5	1.4	.18	
Migration × FR status	0.4	[-5.3, 6.0]	2.8	0.1	.90	
Minority status	-0.4	[-5.6, 4.8]	2.6	-0.2	.88	.04
FR status	2.2	[-1.0, 5.4]	1.6	1.4	.17	
Minority status × FR status	-0.5	[-9.7, 8.8]	4.6	-0.1	.92	
Perceived discrimination	-1.3	[-3.9, 1.2]	1.3	-1.1	.29	.04
FR status	2.7	[-0.5, 5.9]	1.6	1.7	.10	
Perceived discrimination ×FR status	1.4	[-1.7, 4.4]	1.5	0.9	.37	
Social undermining	0.0	[-2.6, 2.7]	1.3	0.0	.97	.04
FR status	2.2	[-0.8, 5.3]	1.5	1.5	.15	
Social undermining × FR status	-1.5	[-5.8, 2.9]	2.2	-0.7	.50	
Ostracism experience	-1.0	[-3.9, 1.9]	1.5	-0.7	.50	.04
FR status	2.2	[-0.7, 5.2]	1.5	1.5	.14	
Ostracism experience × FR status	0.9	[-4.3, 6.2]	2.6	0.4	.72	
Bullying victimization	-0.9	[-3.4, 1.6]	1.2	-0.7	.46	.04
FR status	2.4	[-1.4, 6.1]	1.9	1.3	.21	
Bullying victimization × FR status	1.1	[-3.9, 6.2]	2.5	0.5	.65	
Child abuse	2.0	[-2.3, 6.2]	2.1	0.9	.36	.10
FR status	0.2	[-3.9, 4.2]	2.0	0.1	.93	
Child abuse × FR status	0.0	[-4.8, 4.9]	2.4	0.0	.99	
Trauma	0.0	[-0.6, 0.6]	0.3	0.0	.99	.18
FR status	1.0	[-2.0, 4.0]	1.5	0.7	.51	
Trauma × FR status	1.0	[-0.0, 1.9]	0.5	1.9	.06	

Note. Moderation analysis, parameters are significant if the confidence interval does not contain zero; the significance level of the total models is Bonferroni corrected and significant models would be marked by asterisks; the models for socioeconomic status and trauma contain age as a covariate. FR=familial risk status, BCa CI = bias corrected confidence intervals (based on 5000 bootstrap samples), LLCI = lower limit confidence interval, ULCI = upper limit confidence interval.

risk group, $F(1,106) = 4.13$, $p = .04$, $\eta^2_{partial} = 0.04$, and each risk group showed a non-significant trend towards higher concentrations than the low-risk controls, CR: $F(1,74) = 3.54$, $p = .13$, $\eta^2_{partial} = 0.05$, FR: $F(1,64) = 3.65$, $p = .12$, $\eta^2_{partial} = 0.05$. The results of the other analyses did not change due to the exclusion.

Since two potentially related stressors (traumatic events and child abuse experiences) correlated with hair cortisol concentrations, we also examined the correlation of the two stressors, which was $r = 0.50$, $p < .001$.

4. Discussion

To our knowledge, this study was the first to investigate long-term HPA axis activation by means of hair cortisol concentrations in at-risk groups for psychosis. We did not find stable evidence for a chronic HPA axis hyperactivation in the participants at risk for psychosis. This is at odds with our expectations based on theoretical assumptions (Walker and Diforio, 1997; Walker et al., 2008) and with findings from previous studies in at-risk groups for psychosis, showing higher baseline cortisol levels, enlarged pituitary glands, and smaller hippocampal volumes (for a review see Pruessner et al., 2017).

We chose a low risk threshold in this study and only a small percentage of the participants is likely to develop clinical psychosis (e.g., Kaymaz et al., 2012; Shah et al., 2017). Therefore, the results might imply that HPA axis hyperactivation manifests only later on the trajectory to psychosis. Although it is intuitive to assume a dose-response relationship between clinical risk progression and HPA axis hyperactivation (e.g., Walker et al., 2013), it needs noting however, that we found a small but non-significant effect (tendency towards higher hair cortisol concentrations in the at-risk participants), and previous studies using more stringent risk criteria (indicative of higher risk) mostly also show only small or medium effect sizes (e.g., Carol and Mittal, 2015; Day et al., 2014; Walker et al., 2013). However, the effect size magnitudes for hair cortisol concentrations and salivary cortisol might not be directly comparable. To shed light on this issue, a direct comparison of groups varying in risk status using the same methodology or longitudinal designs are necessary. Furthermore, small effect sizes and the heterogeneous findings in this field of research might be due to the abundance of influencing factors in the measurement of HPA axis indicators. In our study, we were able to control for some of them (e.g., BMI, age, medication, situational influences). The fact that excluding one outlier from LR led to a significant difference between the at-risk participants and LR indicates that we need larger samples with rigorous control of the whole array of potential confounders in order to bring the field further. The rather small effect sizes in the empirical literature might also mirror that HPA axis hyperactivation is only one piece of the multifaceted puzzle of risk for psychosis and probably only captures specific aspects of the stress-related psychopathological processes.

It should also be noted that the majority of the persons with psychotic experiences and close family members of persons with a psychotic disorder do not only have an elevated risk for psychotic disorders but also for a range of other disorders (e.g., McGrath et al., 2016; Shah et al., 2017). Hence, we most probably will have captured a broader range of psychopathological processes, which is also reflected in the fact that some of the participants in the at-risk groups had other mental disorders. Even though there is also evidence for HPA axis hyperactivation in some other mental disorders (e.g., in bipolar disorder, for a meta-analysis see Murri et al., 2016) – indicating possibly a shared vulnerability – this broader risk for psychopathology could also entail further potential confounders for the investigation of HPA axis activation (e.g., in bipolar disorders cortisol levels tend to be higher in manic compared to other phases of the disorder; Murri et al., 2016)

Among the wide range of social stressors known to be associated with an increased risk for psychosis, we found that only the most severe stressors, namely child abuse experiences and traumatic events were predictive of higher hair cortisol concentrations, irrespective of risk status. In the multiple regression model only traumatic events remained a significant predictor, which is not surprising as child abuse experiences were at least partly covered by the measure of traumatic events. This is also supported by the fact that traumatic events and child abuse experiences were substantially correlated ($r = 0.50$, see supplementary analyses). The results thus appear to support our assumption that the exposure to stressors contributes to HPA axis hyperactivation. They are in line with previous studies reporting elevated cortisol levels to be associated with a history of trauma (e.g., Simmons et al., 2016; Steudte et al., 2011) and with studies showing trauma, especially childhood trauma, to be a risk factor for psychotic disorders (e.g., Addington et al., 2013; Krkovic et al., 2018; Varese et al., 2012). The results are also in accordance with the Neural-Diathesis-Stress Model (Walker and Diforio, 1997; Walker et al., 2008), which postulates that prenatal and early stressors lead to a HPA axis hyperactivation. Building on this model, it would be promising to expand the assessment of stressors and to additionally include prenatal stressors (e.g., maternal stress during pregnancy).

The fact that the other social stress measures did not correlate with hair cortisol concentrations could have several reasons: It might imply that the other stressors were not as stressful as that they led to a systematic elevation of hair cortisol concentrations. Then again, the absence of the expected relationship could also be attributable to our way of measuring: Firstly, retrospective recall of stressors can be biased (see also limitation section), which might have weakened the association with hair cortisol concentrations. Secondly, it might be necessary to further specify the timing and duration of the stressor (see e.g., Chrousos, 2009; Miller et al., 2007), which most of our measures did not do.

We also expected the genetic risk for psychotic disorders to moderate the association between social stressors and HPA axis hyperactivation. In contrast to previous studies (Collip et al., 2011; Collip et al., 2013; Cullen et al., 2015), this hypothesis was not confirmed in our study. Thus, our results do not speak for a gene-environment interaction. The overall pattern of findings appears to be more compatible with the assumption that a gene-environment correlation might contribute to the emergence of HPA axis hyperactivation (see van Os et al., 2008 and van Winkel et al., 2013 for a more detailed description of potential gene-environment correlations in the context of psychosis). Severe social stressors were related to hair cortisol concentrations and not only the clinical risk participants but also the individuals at familial risk reported to have experienced more social stressors than the low-risk control group (see Table 2). Even though social stressors, such as childhood trauma experiences are commonly assumed to contribute independently to the emergence of psychosis (Arseneault et al., 2011; Lecei et al., 2019; Trotta et al., 2015), there is also preliminary evidence from longitudinal studies for a bidirectional relationship between pre-existing vulnerability and exposure to stressors (psychosis: Kelleher et al., 2013; mixed psychopathology: Schaefer et al., 2018), and higher exposure to social stressors has been observed in persons with a genetic vulnerability for psychosis (Arseneault et al., 2011; Cullen et al., 2014; Walder et al., 2014; Wigman et al., 2012). For example, a child might be at greater risk of being emotionally neglected as a result of the father's psychotic episode. To conclude, social stress exposure and potential gene-environment correlations should be examined in future studies investigating HPA axis activation in familial risk for psychosis.

4.1. Limitations

It is important to note that we accepted participation up to the age of 65 years. The age in CR samples mostly ranges between 12 and 40 years (Schultze-Lutter et al., 2015). In our sample, two CR participants and seven FR participants were older than 40 years. Even though first-episode psychosis can also occur after the age of 40, a transitioning to clinical psychosis is more likely in younger participants (e.g., Jongsma et al., 2017; Kirkbride et al., 2012). It also should be noted, however, that the decline in psychosis incidence with age is generally found to be flatter in women than in men (e.g., Kirkbride et al., 2012) and that 89% of the at-risk participants older than forty years were women. A second limitation concerns our assessment of the social stressors: For several of the social stress measures (socio economic status, migration, minority status, perceived discrimination, bullying victimization, and child abuse) the psychometric properties have not yet been evaluated systematically. Furthermore, we used a retrospective approach, and retrospective case-control studies are prone to recall bias, which refers to the tendency of persons affected by a disorder (or in our study by a risk for a disorder) to report more exposure to factors such as stressful life events compared to controls (e.g., Hassan, 2005). On the one hand, the at-risk participants might tend to search for explanations of their condition (such as having psychotic-like experiences), on the other hand, controls might underreport their exposure. Hence, the difference in exposure to social stressors between the at-risk groups and low-risk controls might have been overestimated in our study. Finally, the sample size was calculated to detect large to moderate but not small effect sizes, although small effects might be more likely given the high number of factors that add to and characterize an at-risk status.

4.2. Conclusion and outlook

The findings do not confirm that HPA axis hyperactivation is an early vulnerability indicator in people at risk for psychosis. However, the results indicate that a heightened exposure to severe social stressors contributes to HPA axis hyperactivation. We did not find this relationship to be significantly moderated by familial risk for psychosis and thus cannot confirm a gene-environment interaction. Future studies should investigate whether a gene-environment correlation might be involved in the emergence of HPA axis hyperactivation.

Declaration of competing interest

None of the authors have any conflict of interest.

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Contributors

E. Söder and T. M. Lincoln designed the study. E. Söder was responsible for the data collection, data analysis and for writing the first draft of the manuscript. A. Clamor controlled the data analysis. All authors contributed to interpreting the data. Similarly, all authors contributed to the manuscript and have approved the final version.

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