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Relation between self-perceived stress, psychopathological symptoms and the stress hormone prolactin in emerging psychosis

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A R T I C L E I N F O

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A B S T R A C T

Background: Psychosocial stress and the stress hormone prolactin are assumed to play an important role in the pathogenesis of schizophrenia and related psychoses, and have been frequently observed to be increased in antipsychotic-naïve patients with a clinical high risk for psychosis (CHR-P) or first episode of psychosis (FEP). The aim of this study was to further elucidate the relationships between self-perceived stress, psychopathological symptoms and prolactin levels in these patients.
Methods: In this cross-sectional study, 45 healthy controls, 31 CHR-P patients and 87 FEP patients were recruited from two different study centers. Prolactin was measured under standardized conditions between 8 and 10 am. All patients were antipsychotic-naïve and not taking any prolactin influencing medication. Self-perceived stress during the last month was measured with the perceived stress scale (PSS-10) immediately before blood taking.
Results: Both CHR-P and FEP patients showed significantly higher levels of self-perceived stress and prolactin than controls. Hyperprolactinemia (i.e. prolactin levels above the reference range) was observed in 26% of CHR-P and 45% of FEP patients. Self-perceived stress was significantly positively associated with affective symptoms, but not with other symptoms. There was no significant association between self-perceived stress and prolactin levels.
Conclusion: Our results confirm that CHR-P and FEP patients have higher stress levels than healthy controls and frequently have hyperprolactinemia, independent of antipsychotic medication. However, although it is well established that prolactin increases in response to stress, our results do not support the notion that increased prolactin levels in these patients are due to stress.

1. Introduction

There is compelling evidence that psychosocial stress is associated with the development of psychotic symptoms (Holtzman et al., 2013; Mizrahi, 2016; Mondelli, 2014). Many decades ago, Zubin and Spring (1977) proposed the 'stress model of schizophrenia'. They hypothesized that traumatic and stressful life events increased the risk of psychosis (Mayo et al., 2017; Misiak et al., 2017). Many environmental factors that create psychosocial stress have been associated with psychosis (Misiak et al., 2017; Radua et al., 2018). For example, exposure to an urban environment (Fett et al., 2019; Vassos et al., 2012) and belonging to a disadvantaged ethnic minority group (Radua et al., 2018; Selten et al., 2019) seem to increase the risk for psychosis. In addition, recent, acute stress is implicated in triggering psychosis (Bebbington et al., 1993; Lataster et al., 2012). Furthermore, previous research has shown an association between the biological stress parameter cortisol and the severity of positive and nonspecific symptoms in patients with a clinical high risk for psychosis (CHR-P) (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013). Positive correlations between elevated serum prolactin and psychopathological symptoms have been reported in first

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episode psychosis (FEP) (Delgado-Alvarado et al., 2018; Vuk Pisk et al., 2019) as well as in first episode schizophrenia (FES) (El Sayed and Abdalla, 2017; Rajkumar, 2014).

The role of prolactin in emerging psychoses has only recently been more widely acknowledged (Riecher-Rössler, 2017). Prolactin's function as a stress hormone has been neglected for a long time by psychiatrists (Lennartsson and Jonsdottir, 2011; Levine and Muneyyirci-Delale, 2018; Low, 2008; Riecher-Rössler et al., 2013), although it has been shown that prolactin levels increase in response to psychosocial stress. Thus, Lennartson and Jonsdottir (2011) demonstrated that prolactin levels increase in response to acute psychosocial stress induced by the Trier Social Stress Test in healthy volunteers. Animal studies also indicate that prolactin is increased both in response to physical and psychological stress (for review, see Levine and Muneyyirci-Delale, 2018). Hyperprolactinemia (i.e., prolactin above the reference range) in patients with psychosis was traditionally mainly attributed to antipsychotic treatment (Peuskens et al., 2014), because it is well known that first generation antipsychotics, and many new-generation antipsychotics, increase prolactin through D2 receptor blockage (Fitzgerald and Dinan, 2008). However, elevated prolactin levels have also been shown to occur frequently in antipsychotic-naïve CHR-P (Aston et al., 2010; Ittig et al., 2017), FEP (Aston et al., 2010; Del Cacho et al., 2019; Delgado-Alvarado et al., 2018; Ittig et al., 2017; Lally et al., 2017; Riecher-Rössler et al., 2013; Vuk Pisk et al., 2019) and FES patients (Albayrak et al., 2014; El Sayed and Abdalla, 2017; Gonzalez-Blanco et al., 2016; Petrikis et al., 2016). Riecher-Rössler et al. speculated that hyperprolactinemia in these patients might be caused by psychosocial stress associated with emerging illness (Riecher-Rössler, 2017; Riecher-Rössler et al., 2013, 2018). Furthermore, since dopamine is the main prolactin inhibiting factor (Fitzgerald and Dinan, 2008), they speculated that hyperprolactinemia, through a well-known feedback loop, stimulates dopamine and thereby even in itself could trigger psychotic breakdown.

However, until now, little is known about the extent to which self-reported perceived stress relates to the severity of symptoms and to elevated prolactin – as a stress hormone - in emerging psychosis. Our study therefore aimed to investigate the role of self-perceived stress in relation to symptom severity and the biological stress parameter of raised prolactin in CHR-P and FEP patients and in healthy controls (HC). We hypothesized that there would be higher self-perceived stress levels in CHR-P and FEP patients than in HC and that increased self-perceived stress levels are associated with increased symptom severity in patients. Further, we hypothesized that prolactin levels in CHR-P and FEP patients would be higher than in HC and that a positive association exists between self-perceived stress and prolactin independent of diagnostic group.

2. Material and methods

2.1. Study design

In this cross-sectional study, levels of self-perceived stress, prolactin and psychopathological symptoms were assessed in CHR-P and FEP patients and HC. Data were collected in two different study centers: 1) via the ***FePsy*** Clinic at the University of Basel Psychiatric Hospital and 2) via the sector care of Mental Health of Parc Sanitari Sant Joan de Déu/Child and Maternal Hospital of Sant Joan de Déu (Sant Boi/Barcelona; Spain).

The study was approved by the ethics committee of the University of Basel and the research committee of Parc Sanitari Sant Joan de Déu and Ethics Committee Sant Joan de Déu respectively and is conform to the declaration of Helsinki. All participants provided written informed consent.

In both study centers, patients were excluded if they had ever taken antipsychotics or any prolactin-influencing medication. This included cimetidine, famotidine, omeprazole, d-fenfluramine, metoclopramide, domperidone, reserpine, methyldopa, calcium antagonists, cocaine, opioids (codeine and morphine), estrogens, oral contraceptives, anti-androgens, and antirheumatic drugs. Likewise, we excluded all patients with a medical condition potentially influencing prolactin status, such as hypothyroidism or pituitary abnormalities or in whom blood sampling and psychopathological symptom assessment were more than 60 days apart.

2.2. Recruitment of CHR-P and FEP patients in Basel (Switzerland)

CHR-P and part of the FEP data analyzed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen ***(FePsy)*** study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere (Riecher-Rössler et al., 2007, 2009). Participants were recruited for the study via the ***FePsy*** Clinic at the Outpatient Department of the University of Basel Psychiatric Hospital, which was set up specifically to identify and treat individuals in the early stages of emerging psychoses.

Screening was performed with the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008). This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung et al., 1998) and has been shown to have a good interrater reliability ($\kappa = 0.67$) for the assessment of the main outcome category "at risk for psychosis" and a high predictive validity (Papmeyer et al., 2018; Peralta et al., 2019; Riecher-Rössler et al., 2008). Individuals were classified as having a CHR-P, a FEP, or being not at risk for psychosis (usually having other psychiatric disorders).

For this study we included all CHR-P and FEP patients that were recruited for the ***FePsy*** study from April 1, 2014 to September 30, 2017 and had completed the perceived stress scale (PSS-10).

2.3. Recruitment of FEP patients and HC in Parc Sanitari Sant Joan de Déu Barcelona, Spain

HC and part of the FEP data analyzed in this study were collected via the sector care of Mental Health of Parc Sanitari Sant Joan de Déu (adults)/Child and Maternal Hospital of Sant Joan de Déu (adolescents). Patients were included if fulfilling the following criteria: A first episode of psychosis defined as the presence of one of the following symptoms: delusional ideas, hallucinations, disorganized language, catatonic or disorganized behavior, and negative symptoms (alogia, abulia, affective flattening) for at least one week and less than five years since onset, age 14–55 years, Score in Young Mania Rating Scale (YMRS) ≤ 20, and completion of the PSS-10. Patients were recruited from November 1, 2013 to May 31, 2019.

A sample of healthy controls, matched for sex and age, was recruited from trade schools, hospital staff and through advertisements in the same time period. Healthy subjects with a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of illness in the psychotic spectrum were excluded.

2.4. Assessment of self-perceived stress

The self-perceived stress scale, 10-item version (PSS-10; Cohen et al., 1983; Cohen and Williamson, 1988) was completed immediately before blood drawing in order to measure global self-perceived stress. The PSS-10 is the most widely used measure of perceived stress and has been extensively validated (Taylor, 2015). The items of the PSS-10 are designed to assess how unpredictable, uncontrollable, and overloaded respondents find their lives in the last month. Participants are asked to rate the frequency with which they experienced situations as stressful (e.g., "How often have you felt difficulties were piling up so high that you could not overcome them?") on a Likert-type scale with response categories ranging from 1 (Never) to 5 (Very often).

2.5. Prolactin measurement

The patients were asked to avoid stress, sports, physical activity, breast stimulation and smoking for 12 h prior to blood sampling and patient adherence to this was controlled by performing a checklist immediately before blood taking. 7.5 ml whole blood was collected between 8 and 10 am after an overnight fast and 30 min rest.

Blood samples were analyzed in two batches (i.e. one batch for each study center). The **E**lectro**C**hemi**L**uminescence **I**mmuno**A**ssay "ECLIA" (Ref. Number 03203093 190, Roche Diagnostics GmbH D-68305 Mannheim) was used to measure prolactin levels. The method has been standardized against the 3rd IRP WHO Reference Standard 84/500 and hyperprolactinemia in this reference is defined as a value above the 97.5th percentile. For adults (i.e., 18 years and older), the cutoff was 324 mU/l in men and 496 mU/l in women. For teenagers (i.e., 14–17 years), the cutoff was 354 mU/l in boys and 492 mU/l in girls.

2.6. Psychopathology assessment

The Brief Psychiatric Rating Scale Expanded (BPRS-E; Lukoff et al., 1986; Ventura et al., 1993) was used to assess Activation, Positive Symptoms, Negative Symptoms, Affect and Disorganization as defined by the five factor model of Shafer et al. (2017).

2.7. Statistical analyses

All data were analyzed using the R environment for statistical computing (R Core Team, 2019). Differences in sociodemographic and clinical characteristics between CHR-P, FEP, and HC were tested with ANOVA and χ^2 tests.

Prolactin was analyzed both on a continuous and binary scale (i.e., above reference range of corresponding sex vs. within normal range). When analyzing prolactin on a continuous scale, prolactin values were first log-transformed (to accommodate positive skew) and then normalized for men and women separately based on the log transformed reference ranges for healthy men and women. The means and SDs of the log transformed normative samples for men and women were calculated by taking the means of log transformed upper and lower bounds of the reference ranges and by dividing the differences between log transformed upper and lower bounds of the reference ranges by 3.92, respectively. Thus, the normal sex difference in prolactin seen in healthy individuals was partialled out from our continuous prolactin measure before inclusion to the models.

Differences in PSS total and (continuous) prolactin levels of CHR-P, FEP and HC were analyzed using ANOVA. The PSS total score or prolactin levels served as dependent variables and group and study center (Basel and Sant Boi/Barcelona) as independent variables. Group differences in frequencies of hyperprolactinemia were analyzed using a logistic regression model including dichotomized prolactin levels (i.e. elevated vs. normal) as dependent variables and group and study center as independent variables. In case of significant main effects of group, pairwise post-hoc comparisons of the estimated marginal means were conducted using Tukey tests with the R package emmeans (Lenth, 2019).

To analyze the relationship between PSS total and psychopathology, separate linear regression models were fitted for each BPRS scale. The corresponding BPRS scale served as dependent variable and PSS total, group and study center as independent variables. Additionally, an interaction term between group and PSS total was included.

The relationships between (continuous) prolactin levels and PSS total and between hyperprolactinemia (i.e. dichotomized prolactin levels) and PSS total were analyzed using linear and logistic regression models, respectively. In both models, the prolactin measure served as the dependent variable and group (i.e., HC, CHR-P, and FEP) and PSS total as independent variables. The models also included an interaction term between group and PSS total and additionally included study center as a covariate.

Continuous independent variables that were included in interaction terms were centered before inclusion to the models to make results more interpretable.

3. Results

3.1. Sample description

We included 31 CHR-P and 16 FEP patients from Basel and 71 FEP patients and 45 HC from Parc Sanitari Sant Joan de Déu Barcelona. A flow diagram for study selection in Basel is shown in Supplementary Fig. 1. Sociodemographic as well as clinical sample characteristics of the included individuals are presented in Table 1.

3.2. Perceived stress and prolactin levels in CHR-P, FEP and HC

There was a significant main effect of group (i.e., HC, CHR-P, FEP) on PSS total ($F = 28.1$, $p < 0.001$). Post hoc tests revealed that HC had a significantly lower score on the PSS total than CHR-P ($t = 3.23$, $p = 0.004$) and FEP patients ($t = 7.46$, $p < 0.001$). There was no significant difference in PSS total between CHR-P and FEP patients ($t = 0.82$, $p = 0.693$) (see Fig. 1).

There was also a significant main effect of group on log and z-transformed prolactin levels ($F = 6.95$, $p = 0.001$). Post hoc tests showed that HC had significantly lower prolactin levels than CHR-P ($t = 2.40$, $p = 0.046$) and FEP patients ($t = 3.69$, $p = 0.001$). There was no significant difference in prolactin levels between CHR-P and FEP patients ($t = 0.54$, $p = 0.853$) (see Fig. 2).

When prolactin was analyzed on a binary scale (i.e., elevated vs. normal), there was again a significant main effect of group (Likelihood ratio [LR] $\chi^2 = 15.7$, $p < 0.001$). This was due to more frequent hyperprolactinemia in CHR-P (Odds ratio [OR] = 12.25, $p = 0.027$) and FEP patients (OR = 5.03, $p < 0.001$) as compared to HC. Percentages of

Table 1
Sociodemographic and clinical sample characteristics.

	HC	CHR-P	FEP	*p*-value
	N = 45	N = 31	N = 87	
Sex:				0.003
Women	21 (46.7%)	3 (9.68%)	31 (35.6%)	
Men	24 (53.3%)	28 (90.3%)	56 (64.4%)	
Age	28.0 (10.2)	23.7 (4.82)	25.7 (9.15)	0.111
Center:				<0.001
Barcelona	45 (100%)	0 (0.0%)	71 (81.6%)	
Basel	0 (0.0%)	31 (100%)	16 (18.4%)	
Antidepressants currently	0 (0.0%)	6 (19.4%)	2 (2.30%)	0.001
Cannabis use in last 3 months	4 (8.89%)	9 (39.1%)	37 (44.0%)	<0.001
BPRS Activation		3.74 (1.39)	4.96 (2.88)	0.026
BPRS Positive Symptoms		4.63 (1.91)	11.4 (3.85)	<0.001
BPRS Negative Symptoms		4.35 (1.89)	6.51 (3.68)	0.002
BPRS Affect		6.58 (3.17)	6.53 (3.48)	0.945
BPRS Disorganization		3.58 (0.99)	6.16 (2.89)	<0.001
BPRS total		36.2 (7.98)	55.9 (17.5)	<0.001

CHR-P = Clinical High Risk of Psychosis; FEP = First Episode Psychosis, HC = Healthy Controls, BPRS = Brief Psychiatric Rating Scale. Numbers are means and standard deviations (SD) for continuous variables and absolute number and percentages for categorical variables.

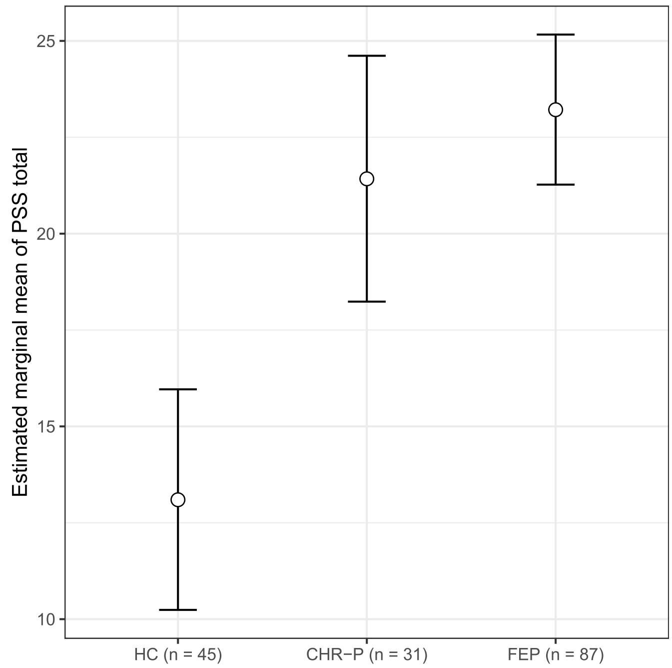

Fig. 1. Estimated marginal means of Perceived Stress Scale (PSS) total scores in healthy controls (HC), patients with a clinical high-risk for psychosis (CHR-P) and patients with a first episode of psychosis (FEP).

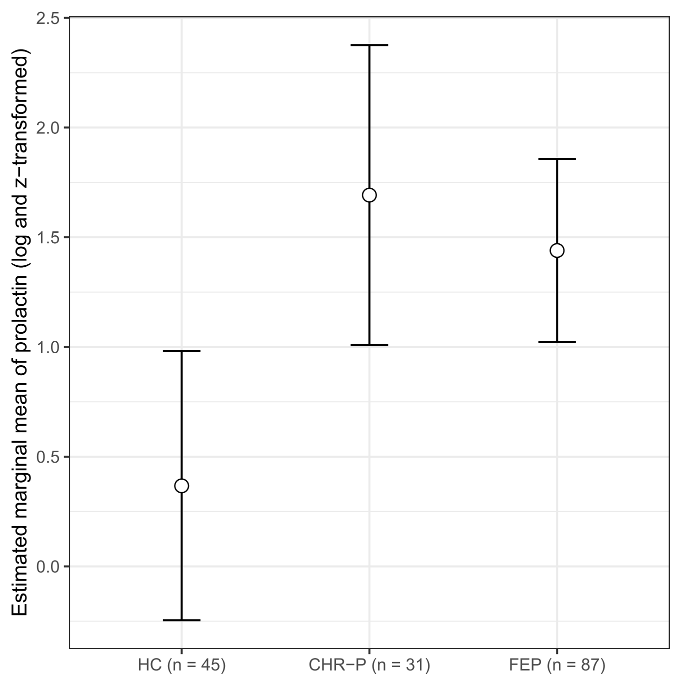

Fig. 2. Estimated marginal means of log and z-transformed prolactin levels in healthy controls (HC), patients with a clinical high-risk for psychosis (CHR-P) and patients with a first episode of psychosis (FEP).

hyperprolactinemia, as well as mean, median and range of log and z-transformed prolactin values for each group and sex are shown in Table 2.

3.3. Relationship between perceived stress and psychopathology

We found a significant association of the PSS total score with the BPRS subscale Affect (β = 0.97; t = 2.17; p = 0.032), but no significant association with any other BPRS subscale (i.e., Positive Symptoms, Negative Symptoms, Disorganization, Activation). There were also no significant interactions between PSS total and group.

3.4. Relationship between perceived stress and prolactin levels

There was no significant main effect of PSS total on (continuous) prolactin levels ($F = 0.55$, $p = 0.458$) and no significant interaction between PSS total and group ($F = 2.04$, $p = 0.133$) (see Fig. 3). There was also no significant interaction between PSS total and sex within the FEP group ($F = 0.01$, $p = 0.921$), indicating that the relationship between self-perceived stress and prolactin levels was not moderated by sex.

When prolactin was analyzed on a binary scale (i.e. elevated vs. normal), there was again no significant main effect of PSS total (LR $\chi^2 = 1.47$, $p = 0.225$) and no significant interaction between PSS total and group (LR $\chi^2 = 2.58$, $p = 0.275$). These results did also not change when prolactin was not corrected for the normal biological variation between the sexes and sex was included as covariate instead.

4. Discussion

In this study the role of self-perceived stress and its relation to psychopathological symptoms and prolactin in emerging psychosis was investigated in 31 antipsychotic-naïve CHR-P and 87 FEP patients, as well as in 45 HC. In line with our hypotheses, we could show increased self-perceived stress and prolactin levels in both CHR-P and FEP patients as compared to HC. Furthermore, we could demonstrate a positive association between self-perceived stress and affective symptoms (i.e., symptoms of anxiety and depression) in CHR-P and FEP patients. However, in contrast to our hypotheses, we could not show a positive relationship between self-perceived stress and other psychopathological symptom dimensions, such as positive and negative symptoms, disorganization, and activation. Furthermore, there was no significant association between self-perceived stress and the biological stress parameter prolactin in the total group and there was no indication that this association was moderated by group.

The increased self-perceived stress levels in both CHR-P and FEP patients as compared to HC is in agreement with previous research, as increased self-perceived stress has repeatedly been found in both CHR-P (Gattere et al., 2018; Labad et al., 2015; Palmier-Claus et al., 2012) and FEP patients (Allott et al., 2015; Del Cacho et al., 2019; Mondelli et al., 2010). We also found that CHR-P show similar levels of self-perceived stress as FEP patients. To our knowledge, only one further study has directly compared stress levels between CHR-P and FEP patients finding that CHR-P are even more stressed than FEP patients (Pruessner et al., 2011). The reason for this discrepancy might be that our study has measured self-perceived stress during the last month using the PSS-10, whereas the other has used the Trier Inventory for Chronic Stress (TICS), which measures stress during the last 3 months (Schulz and Schlotz, 1999).

Consistent with a large body of evidence (Labad, 2019; Riecher-Rössler, 2017), we also found that hyperprolactinemia frequently occurs in CHR-P and FEP patients, independent of D2-receptor blockage of antipsychotic medication. Specifically, 26% and 45% of antipsychotic-naïve CHR-P and FEP patients, respectively, presented with hyperprolactinemia in this study, which is similar to results from other recent studies in antipsychotic-naïve CHR-P (Aston et al., 2010; Ittig et al., 2017) and FEP patients (Aston et al., 2010; Del Cacho et al., 2019; Delgado-Alvarado et al., 2018; Ittig et al., 2017; Lally et al., 2017; Riecher-Rössler et al., 2013; Vuk Pisk et al., 2019). Since hyperprolactinemia can have severe consequences, including amenorrhea, galactorrhea, an acceleration of osteoporosis in women and a lack of libido and erectile dysfunction in men, our results reinforce the need for increased clinical attention and assessment of prolactin levels in patients with emerging psychoses (Riecher-Rössler, 2017). Furthermore, the

Table 2
Prolactin values in antipsychotic-naïve CHR-P and FEP patients and HC.

	HC		CHR-P		FEP	
	Women N = 21	Men N = 24	Women N = 3	Men N = 28	Women N = 31	Men N = 56
Prolactin mU/l						
Mean (SD)	399 (218)	228 (103)	647 (18)	258 (118)	720 (856)	353 (183)
Median	357	211	650	226	437	319
Range	143–1050	124–505	627–663	103–581	77–4092	93–780
Hyperprolactinemia						
n (%)	5 (23.8%)	3 (12.5%)	3 (100%)	5 (17.9%)	13 (41.9%)	26 (46.4%)
Prolactin normalized						
Mean (SD)	1.14 (1.22)	0.65 (1.16)	2.62 (0.07)	1.03 (1.24)	1.82 (2.08)	1.73 (1.60)
Median	1.14	0.62	2.63	0.89	1.65	1.8
Range	−1.12 - 3.82	−1.15 - 3.27	2.54–2.68	−1.43 - 3.69	−1.99 - 6.48	−1.73 - 4.45

CHR-P = Clinical High Risk for Psychosis, FEP = First episode psychosis, HC = Healthy Controls.

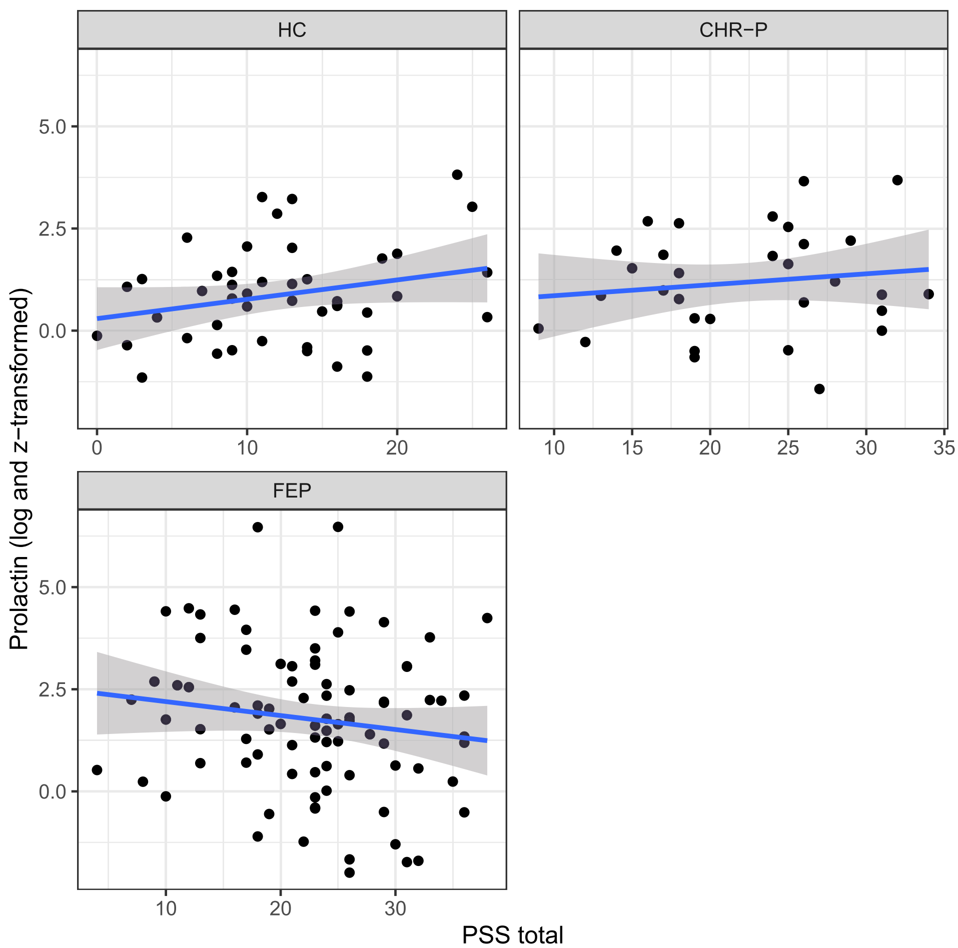

Fig. 3. Correlations between log and z-transformed prolactin levels and Perceived Stress Scale (PSS) total scores in healthy controls (HC), patients with a clinical high-risk for psychosis (CHR-P) and patients with a first episode of psychosis (FEP).

high percentage of patients with hyperprolactinemia in the at-risk stage as well as in the first episode stage suggests this to be a relatively stable marker of emerging disease.

Regarding relationships between self-perceived stress and psychopathological symptoms, our results are also consistent with previous literature. While, to our knowledge, these relationships have not been investigated in CHR-P patients, both of two studies investigating these relationships in FEP patients found that self-perceived stress was positively associated with depressive symptoms, but not with positive and negative symptoms (Garner et al., 2011; Renwick et al., 2009). Studies in other patient populations and in healthy controls have also consistently demonstrated positive associations between self-perceived stress, as measured by the PSS-10, and affective symptoms, such as depression and anxiety (for review, see Lee, 2012). This finding is also in agreement with Cohen et al. (1983) who reported that "there is some overlap between what is measured by depressive symptomatology scales and measured by the PSS, since the perception of stress may be a symptom of depression".

Regarding the association between self-perceived stress and prolactin levels, our results concur with previous research. To our knowledge, only two studies have analyzed the correlation between self-perceived stress and prolactin levels in antipsychotic-naïve FEP (Del Cacho et al., 2019; Lally et al., 2017) and only one study in CHR-P patients (Labad et al., 2015). These studies did not detect a significant relationship between self-perceived stress, as measured by the PSS, and prolactin levels. Furthermore, in another study investigating newly admitted patients with acute psychosis (Mazure et al., 1997), prolactin levels were not found to be related to recent life stressor severity. Hence, although it is well established that prolactin increases in response to acute physical and psychological stress (Levine and Muneyyirci-Delale, 2018), existing data do not support the assumption that increased prolactin levels frequently observed in antipsychotic-naïve patients with emerging psychosis are directly due to stress. Several alternative explanations have therefore been put forward to explain the increased prolactin levels in these patients (Labad, 2019). As Riecher-Rössler (2017) has suggested, the increased prolactin levels in many patients with emerging psychosis might relate to the underlying pathogenetic process in at least a subgroup of patients. For example, it has been speculated that hyperprolactinemia might be secondary to an altered prolactin regulation, as one study with drug-naïve FEP patients has shown an altered response to low doses of thyrotropin-releasing hormone (TRH), suggesting a hypersensitive prolactin-stimulating system (Spoov et al., 2010). Others suggested that elevated prolactin levels are related to the upregulated inflammatory status in this patient population (Song et al., 2014) since prolactin is one of the mediators of the bidirectional communication between neuroendocrine and immune systems (Cejkova et al., 2009) and since inflammatory processes are increasingly recognized to play an important role in the pathogenesis of schizophrenic psychoses (Khandaker et al., 2015; Khoury and Nasrallah, 2018).

This study has the following strengths and limitations. First, all included patients were antipsychotic-naïve and prolactin was measured under controlled conditions to avoid prolactin-influencing variables, such as the acute effects of nicotine (Xue et al., 2010), diurnal cycle, and acute stress induced by blood sampling. Second, by combining patients from two different centers, we were able to obtain a larger sample size than most previous studies. However, the group of CHR-P patients was considerably smaller than the group of FEP patients, leading to decreased statistical power in group comparisons involving the CHR-P group. Furthermore, although post-hoc power analyses for the main effects of interests revealed that we had achieved sufficient power to detect medium effect sizes, this was not the case for small effect sizes. Hence, it is possible that non-significant results were due to insufficient power to detect small effect sizes. Third, self-perceived stress was only measured for a time frame of one month. We therefore cannot rule out the possibility that self-perceived stress measures with a narrower or longer time frame would be differently associated with prolactin levels. Fourth, we did not analyze other biological measures of stress, such as cortisol, in this study. Fifth, due to the small number of female patients, we were also not able to investigate whether the association between self-perceived stress and prolactin is moderated by sex in the CHR-P group or whether it is dependent of the menstrual cycle within women. A further limitation of our study is the cross-sectional study design. A prospective study design with repeated measurements of self-perceived stress, psychopathological symptoms and prolactin would have been better able to disentangle the complex relationships between these variables in emerging psychoses. Future studies should also include other patient populations, such as patients with affective disorders, to investigate the diagnostic specificity of our results.

Taken together, our results provide further evidence that CHR-P and FEP patients show increased self-perceived stress and prolactin levels, independent of D2-receptor blockage of antipsychotic medication. Despite increased self-perceived stress levels and a large body of evidence from animal and human research showing that prolactin increases in response to stress (Levine and Muneyyirci-Delale, 2018), we could not demonstrate an association between self-perceived stress and prolactin levels in patients with emerging psychosis. This result seeks replication and if confirmed further explanation.

Contributors

Anita-Riecher-Rössler, Sarah Ittig, Nuria Del Cacho, and Judith Usall designed the study and wrote the protocol. Erich Studerus and Sarah Ittig undertook the statistical analysis and wrote the first draft of the manuscript. Anita Riecher-Rössler, Katharina Beck, Sarah Ittig, Nuria Del Cacho, Regina Vila- Badia, and Anna Butjosa were involved in recruitment of patients and data collection. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.06.014.

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