Cortisol stress response in psychosis from the high-risk to the chronic stage:

A systematic review

Running title: Cortisol stress response in psychosis

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Abstract

Objectives

We review studies of whether cortisol levels following psychosocial stress exposure differ between patients with psychosis and healthy control subjects.

Methods

Original research published between 1993 and February 2019 was included in the literature search. Studies that used experimentally-induced psychosocial stress and reported stress response measures of plasma or saliva cortisol levels in patients at any stage of illness (i.e. high risk, first episode and chronic phase) were included.

Results

A total of 17 studies were included. Although there was evidence of inconsistencies in measures, we observed moderate evidence of an association with stress-induced cortisol blunting response across studies.

Conclusions

This review highlights recent evidence of blunting of cortisol response following experimentally-induced psychosocial stress. While there was some evidence of this blunted response across illness types and stages, the strongest evidence was observed for those with chronic schizophrenia. Due to the low number of studies, in particular in bipolar disorder, much work is still needed to accurately characterise the biological effects of stress in psychosis.

Keywords: Cortisol; stress response, stress reactivity; HPA axis; bipolar disorder; schizophrenia, psychosis

1. Introduction

Current and lifetime stress is widely acknowledged to contribute to risk for, and variation in, symptom severity in mental health disorders. In psychosis spectrum disorders, the contribution of stress and adversity during childhood and adolescence is now also considered to contribute to clinical presentation. However, despite progress in identifying some of the genetic architecture of these disorders, modelling the interaction between genetic risk and environmental factors is still at an early stage. Towards this end, understanding the biological mechanisms by which both current and life time stress exposure exert an effect represents an important research goal. Borrowing from recent research in affective disorders (Ciufolini et al., 2014, Zorn et al., 2017), one potential mechanism is the effect of acute psychosocial stressors on cortisol response in psychosis.

The neural diathesis-stress model of schizophrenia has been proposed as a framework for the development of schizophrenia as the consequence of an interaction between a genetic susceptibility and stress triggered by stressful or traumatic experiences (Pruessner et al., 2017, Walker et al., 2008, Walker and Diforio, 1997). Briefly, this theory is based on findings that the hypothalamus-pituitary-adrenal (HPA) axis is activated after stress exposure and that cortisol as one of many secretagogues and glucocorticoids released throughout the brain. Importantly, this model posits that hippocampal structure and function as well as the activation of the subcortical dopamine system are altered by HPA activation or resulting cortisol release which affect behavioral outcome, including cognitive deficits in psychosis.

One of the principal means of assessing the effects of stress exposure on the HPA axis is via laboratory-induced psychosocial stress tasks, which, as a proxy to psychosocial stress in daily life, have the advantage of experimental control (Allen et al., 2014). The purpose of these stress

tasks, such as the Trier Social Stress Task (TSST), is to study the individual stress response which is known to induce the HPA axis (Kirschbaum et al., 1993) among other neurobiological systems (Joels and Baram, 2009). The TSST is the most widely established laboratory-induced psychosocial stress task, which consists of an anticipation period (ten mins) and a test period (ten mins) (Kirschbaum et al., 1993). During the test period, participants are asked to give a free talk (five mins) and to perform a mental arithmetic task (five mins) in front of jury members. At the same time, participants' verbal and non-verbal behaviour is video recorded.

Cortisol is one of the most commonly investigated HPA axis hormones in the field of psychosocial stress due to its ease of being assayed in blood, saliva, urine and hair. Out of these, the measurement of cortisol in saliva is the most frequently reported HPA axis biological stress response measure. To date, only a limited number of reviews has been conducted to examine the role of stress and its effects on the HPA axis in schizophrenia over the course of the illness (Pruessner et al., 2017, Walker et al., 2008) and patients with first-episode psychosis (Borges et al., 2013). Two systematic reviews and meta-analyses have been carried out to compare differences between schizophrenia and depression in TSST-induced cortisol stress response based on chronic schizophrenia patients (Ciufolini et al., 2014, Zorn et al., 2017). Finally, one systematic review focused on the effects of the TSST on heart rate and cortisol stress responses across schizophrenia spectrum disorders at the first-episode and chronic stages of the illness (Lange et al., 2017a).

These previous systematic reviews and meta-analyses have variously proposed that the HPA axis response to psychosocial stress is blunted at the first-episode of schizophrenia based on one included study (Lange et al., 2017a) and in chronic schizophrenia (Ciufolini et al., 2014, Lange et al., 2017a, Zorn et al., 2017). However, given the small numbers available at the time

for these reviews, these conclusions should be considered as preliminary. Furthermore, no studies at the high-risk stage of schizophrenia were included due to a lack in the literature in the previous reviews. The purpose of the present review was to carry out the most comprehensive systematic review undertaken to date of acute psychosocial stress exposure effects on cortisol levels across psychotic disorders. In particular, this systematic review expands the scope of the previous reviews by including studies on the high-risk stage in psychotic disorders beyond schizophrenia spectrum disorders. In doing so, we hoped to clarify whether changes in cortisol response are observed already at the high-risk stage and if so whether these changes are relevant for patient groups with psychosis or only with schizophrenia.

2 Methods

2.1 Literature search strategy

We conducted a systematic literature search using PubMed and PsycINFO for original papers that studied cortisol stress response around the time of a laboratory-induced psychosocial stress task (or an equivalent stress task) in patients with schizophrenia, bipolar disorder and psychosis, which were published between 1993 and February 2019. We used combinations of the following key terms: ((cortisol OR cortisol reactivity OR cortisol response OR Hypothalamus-pituitary adrenal OR HPA OR Hypothalamus-pituitary adrenal axis OR HPA axis OR HPA axis reactivity OR HPA axis response) AND (stress OR social stress OR social trauma OR psychosocial OR TSST OR Trier OR Trier Social Stress Task) AND (schizophrenia OR bipolar disorder OR psychosis OR psychotic)). We included only studies that used a psychosocial stress task that included laboratory-induced stress manipulation in form of uncontrollability (for example, time pressure or impossible task to solve) and/or social evaluation (for example, speech in front of a jury or video recording) in adult individuals at high risk of developing schizophrenia, bipolar disorder or psychosis or in patients with schizophrenia, bipolar disorder and psychosis. Studies that investigated the effect of chronic stress, long-term stress exposure, recent stress level, exam stress, studies that investigated the HPA axis reactivity after pharmacological challenges (for example, the dexamethasone suppression test and the corticotropin-releasing hormone stimulation test), studies reporting adrenocorticotropic hormones only as well as systematic reviews were excluded. Studies were also searched through references of selected articles.

2.2 Inclusion criteria

Identified studies were screened and selected for inclusion using the following criteria: (1) Original and peer-reviewed articles published in an English language journal, (2) Adult

individuals at high risk of developing schizophrenia, bipolar disorder or psychosis were included; (3) Adult patients with schizophrenia, bipolar disorder or psychosis, and/or healthy participants were included; (4) Data on laboratory-induced acute psychosocial stress were reported; (4) Data on plasma cortisol, salivary cortisol or free cortisol assayed with an established hormone assay were reported; and (5) Data on HPA axis activity after the laboratory-induced psychosocial stress task were reported.

2.3 Study characteristics

The literature search identified 2297 studies in total, of which 13 studies were original studies that matched the study criteria. Four additional studies were identified through review of references of these papers. The PRISMA flow diagram is presented in Figure 1 which displays the number of included and excluded studies as well as the reasons for exclusion. Therefore, in total 17 studies were included.

Figure 1. Flow diagram selection of study process

3 Results

The included studies were grouped based on the illness stage, diagnosis and study characteristics. The main findings are reported in Table 1.

Five high-risk for psychosis studies were included. Out of these, two studies examined the cortisol stress response in siblings and relatives of individuals with schizophrenia (van Leeuwen et al., 2018) and in individuals at ultra-high risk of psychosis (Pruessner et al., 2013). Two other studies recruited and tested siblings and patients with chronic schizophrenia (Kother et al., 2018) and patients with chronic psychosis (Lincoln et al., 2015). In the fifth study, siblings and patients with bipolar disorder were studied (Houtepen et al., 2015).

Two studies investigated the effect of the psychosocial stress task on cortisol levels in first-episode patients (Seitz et al., 2019, van Venrooij et al., 2012).

Ten studies were included for the group of studies in patients with chronic psychosis (Lange et al., 2017b, Rubio et al., 2015, Nugent et al., 2015, Brenner et al., 2011, Brenner et al., 2009, Jansen et al., 2000, Jansen et al., 1998, Tas et al., 2018, Steen et al., 2011, Wieck et al., 2013). Among these studies, study overlap was observed between Brenner et al. 2009 and Brenner et al. 2011 (Brenner et al., 2009, Brenner et al., 2011), however different outcome measures for the cortisol stress reactivity were reported.

Table 1. Study characteristics and main findings

Study	Participants	Sex (Male : Female)	Age (Mean / SD)	Type of stressor	Time of testing	Sample type	Main findings
Studies of high-risk for psychosis							
van Leeuwen et al., 2018	Sib = 40 HP = 40	Sib = All men HP = All men	Sib = 32.5 (4.80) HP = 7.4/34.8 (9.1)[1]	Modified TSST	Afternoon and evening	Saliva	• No group difference in cortisol levels at baseline • No group differences in stress-induced cortisol levels at anticipation, peak or recovery phases
Kother et al., 2018	Rel = 24 SZ = 35 HP = 28	Rel = 13 : 11 SZ = 21 : 14 HP = 17 : 11	Rel = 42.17 (14.26) SZ = 41.03 (12.18) HP = 35.75 (14.83)	Video recorded speech	Afternoon and evening	Saliva	• No group difference in cortisol levels at baseline • No group differences in stress-induced cortisol levels at anticipation, peak or recovery phases
Houtepen et al., 2015	Sib = 27 BP = 49 HP = 48	Sib = 21 : 6 BP = 25 : 24 HP = 25 : 23	Sib = 54.5 (32-66)[4] BP = 43.4 (19-67) HP = 43.5 (21-69)	TSST for groups	Afternoon	Saliva	• No group difference in cortisol levels at baseline • Significantly decreased cortisol stress response from 20 min after TSST until the end of measurement in BP compared to Sib and HP
Lincoln et al., 2015[6]	Rel = 26 PSY = 35 HP = 28	Rel = 13 : 13 PSY = 20 : 15 HP = 17 : 13	Rel = 41.7 (11.1) PSY = 40.5 (12.5) HP = 34.9 (14.4)	Video recorded speech	Afternoon and evening	Saliva	• No group differences in stress-induced cortisol levels at anticipation, peak or recovery phases
Pruessner et al., 2013	UHR = 21 HP = 21	UHR = 12 : 9 HP = age-matched[5]	UHR = 20.8 (3.27) HP = 20.8 (3.10)	TSST	Afternoon	Saliva	• Significantly blunted increase of cortisol levels during anticipation and peak phase in UHR compared to HP

Studies of first episode psychosis							
Seitz et al., 2019	FEP = 57 HP = 43	FEP = 41 : 16 HP = 23 : 20	FEP = 23.9 (3.8) HP = 23.2 (3.9)	Modified TSST	Afternoon	Saliva	• Significantly lower cortisol levels during the TSST in FEP compared to HP • Significantly lower AUCg levels for cortisol in FEP compared to HP • No group difference for cortisol increase (AUCi)
van Venrooij et al., 2012	FEP[3] = 10 HP = 15	FEP = All men HP = All men	FEP = 23 (19 – 29) HP = 22 (20 – 25)[4]	Public speaking test	Morning – early afternoon	Blood	• No group difference in cortisol levels at baseline • Significantly lower cortisol levels in FEP compared to HP as interaction effect
Studies of chronic psychosis							
Tas et al., 2018	SZ = 32	SZ= 15 : 17	34.07 (8.53)	Modified TSST	All day	Blood	• Cortisol response group (n = 11) showed a mean percentage increase in cortisol after the TSST compared to baseline • Cortisol non-response group (n = 21) showed a mean percentage decrease in cortisol after the TSST compared to baseline • No group difference in cortisol levels at baseline between cortisol response group and non-response group

Lange et al., 2017b	SZ = 25 HP = 25	SZ = 18 : 7 HP = 16 : 9	SZ = 38.3 (13.5) HP = 41.16 (11.1)	TSST	Afternoon	Saliva	• Significantly decreased cortisol levels in patients compared to HP at baseline, anticipation, peak or recovery phases • Significantly decreased AUCi and AUCg values in patients compared to HP
Nugent et al., 2015	SZ = 45 HP =53	SZ = 29 : 16 HP = 30 : 23	SZ = 37.6 (11.6) HP =38.4 (12.8)	Psychological distress challenge tasks	Afternoon	Saliva	• No group difference in cortisol levels at baseline • No group differences in stress-induced cortisol levels at anticipation, peak or recovery phases
Rubio et al., 2015	SZ = 58 HP = 28	SZ = All men HP = All men	SZ = 36.3 (6.4) HP = 36.6 (6.3)	Socially-evaluated cold-pressor test	Afternoon	Saliva	• No group difference in cortisol levels at baseline • Significant main effect of interaction between reduced cortisol levels post stress test in SZ compared to HP
Wieck et al., 2013	BP = 13 HP = 15	BP = All women HP = All women	BP = 46.36 (10.86) HP = 48.07 (10.63)	TSST	Not reported	Saliva	• No group difference in cortisol levels at baseline • Significantly decreased AUC cortisol response in BP compared to HP
Brenner et al., 2011	SZ = 30 HP = 29	SZ = 24 : 6 HP = 21 : 8	SZ = 30.5 (7.3) HP = 29.3 (8.1)	Modified TSST	Afternoon	Saliva	• No group difference in cortisol levels at baseline or AUCi
Steen et al., 2011	SZ = 70 BP = 81 HP = 96	SZ = 40 : 30 BP = 33 : 48 HP = 52 : 46	SZ (male) = 25.5 (11.0) SZ (female) = 29.5 (15.0) BP (male) = 36.0 (24.0) BP (female) = 33.0 (18.0) HP (male) = 32.0 (15.0) HP (female) = 31.5 (14.0)	Mental challenge task	Morning	Saliva	• No group differences at baseline • Significant group difference in % reduction in cortisol in HP when compared to all patients (SZ and BP combined) but not

							between HP versus SZ or HP versus BP • No group difference in cortisol change between SZ and BP
Brenner et al., 2009	SZ = 30 HP = 29	SZ = 24 : 6 HP = 21 : 8	SZ = 30.5 (7.3) HP = 29.3 (8.1)	Modified TSST	Afternoon	Saliva	• No group difference in cortisol levels at baseline • SZ and HP differ from each other in terms of smaller change in cortisol between baseline and 15 min post-TSST.
Jansen et al., 2000[5]	SZ = 18 HP = 21	SZ = 11 : 7 HP = 13 : 8	SZ = 27.7 (4.3) HP = 27.0 (5.4)	Psychosocial task	All day	Saliva	• No group difference in cortisol levels at baseline • Decreased cortisol response to task in SZ compared to HP
Jansen et al., 1998	SZ = 10 HP = 10	SZ = All men HP = All men	SZ = 27.1 (7.0) HP = 26.9 (5.8)	Public speaking test	All day	Saliva	• No group difference in cortisol levels at baseline • Significant interaction effect for cortisol response with decreased cortisol response in SZ compared to HP

[1] Data reported for subjects in experimental group.
[2] Data reported for patients with schizophrenia, first-degree relatives and healthy participants and the social stress condition only.
[3] Diagnosis of schizophrenia (7 patients) and psychotic disorder in the schizophrenia spectrum (3 patients)
[4] Median and range reported.
[5] Data reported only for psychosocial task.
[6] Data not reported.
[7] Data reported for patients with psychosis, first-degree relatives and healthy participants and the social stress condition only.

Abbreviations: AUC, area under the curve; AUCg, area under the curve with respect to ground; AUCi, area under the curve with respect to increase; BP, bipolar disorder; FEP, patients with first-episode psychosis; HP, healthy participants; PSY, patients with psychosis; Rel, first-degree relatives; Sib, first-degree siblings; SZ, patients with schizophrenia; TSST, Trier Social Stress Task; UHR, Ultra – high risk subjects.

3.1 Studies of high-risk for psychosis

To date, only two studies have investigated cortisol stress reactivity in first-degree siblings of patients with schizophrenia (van Leeuwen et al., 2018) and individuals at ultra-high risk of psychosis (Pruessner et al., 2013). A mixed pattern of results was observed for both studies: While the salivary cortisol levels were not significantly different between siblings and healthy control subjects (van Leeuwen et al., 2018), individuals at ultra-high risk of psychosis showed significantly blunted increase of cortisol levels during the anticipation and phases around the time of the modified TSST in contrast to healthy participants (Pruessner et al., 2013). Furthermore, Pruessner et al. 2013 reported a post-hoc finding of significant negative correlation between reduced cortisol levels and higher perceived recent stress levels as assessed with retrospective self-report in ultra-high risk individuals of psychosis (Pruessner et al., 2013). The lack of a group difference in a cortisol stress response between siblings and healthy controls contrasts to the observed stress response as measured with brain functional activity in regions implicated in the default-mode network and salience network after the stress exposure in the at-risk individuals versus healthy controls (van Leeuwen et al., 2018).

When comparing the findings between siblings and patients with schizophrenia or psychosis, Kother et al. 2018 found no differences between the groups at either the anticipation, peak or recovery phases around the time of the stress challenge (Kother et al., 2018). This finding is in keeping with the Lincoln et al. 2015 study in which first-degree relatives of patients with psychosis did not display any significantly different stress-induced cortisol levels around the time of a video recorded speech when compared to patients with chronic psychosis and control subjects (Lincoln et al., 2015).

In the fifth study, patients with bipolar disorder showed a reduced cortisol stress response when compared to healthy participants and first-degree siblings (Houtepen et al., 2015). In this study, the modified TSST version, the group version of the TSST, was utilised (Houtepen et al., 2015) which makes a direct comparison difficult.

3.2 Studies of first episode psychosis

Two studies examined the cortisol stress response to a laboratory-induced stress challenge in patients with first-episode schizophrenia (van Venrooij et al., 2012) and first-episode psychosis (Seitz et al., 2019). Both studies reported significantly reduced plasma cortisol levels in patients when compared to healthy participants. Moreover, Seitz et al. 2019 reported significant positive correlations between lower AUCg cortisol levels and reduced self-esteem, lower active coping in addition to a significant negative correlation between these reduced AUCg cortisol levels and increased levels of perceived stress levels around the time of the modified TSST (Seitz et al., 2019). Furthermore, cortisol no-responders in the first-episode patient group reported significantly higher levels of physical neglect as measured with the Childhood Trauma Questionnaire (CTQ) (Seitz et al., 2019).

3.3 Studies of chronic psychosis

A mixed pattern of cortisol stress responses was found when patients with chronic psychosis were compared: Out of eight studies with a healthy control group, seven studies reported a blunted cortisol response in patients with schizophrenia when compared to healthy participants (Lange et al., 2017b, Rubio et al., 2015, Brenner et al., 2009, Jansen et al., 1998, Jansen et al., 2000, Wieck et al., 2013, Steen et al., 2011), whereas two studies observed no group differences (Nugent et al., 2015, Brenner et al., 2011). Three out of the five studies suggesting a blunted cortisol stress response in patients are early studies from the same group after using a

modification of the TSST that did not include video recording during the speech. Two more recent studies reported reduced cortisol levels in patients when contrasted to healthy participants, in which the modified TSST (Lange et al., 2017b) and the socially evaluated cold-pressor task were used (Rubio et al., 2015), in contrast to the traditional TSST. In addition, Lange et al. 2017b observed a significant positive correlation between greater severity of positive symptoms measured with the Positive and Negative Symptom Scale and lower cortisol values as measured with area under the curve with respect to increase (AUCi) (Lange et al., 2017b). From the same study, the authors reported also findings of significantly higher levels of exposure to emotional abuse as retrospectively assessed with the CTQ in patients who showed a cortisol stress response after the TSST only.

Brenner et al. 2011 reanalysed their findings from the previous publication (Brenner et al., 2009) on a proposedly blunted cortisol stress response and reinterpreted their findings with no significant group differences referring to the AUCi findings (Brenner et al., 2011). These findings of lack of group differences from the Brenner et al. 2011 study are in keeping with Kother et al. 2018 and Nugent et al. 2015 (Kother et al., 2018, Nugent et al., 2015) despite the fact that these studies did not utilise comparable psychosocial stress tasks (these differed in terms of the levels of task controllability and social evaluation). Furthermore, Nugent et al. 2015 observed a significant diagnosis by distress intolerance interaction based on aborting the stress task in patients only in addition to a significant negative association between increased post-stress cortisol level change and decreased white matter integrity as measured with Diffusion Tensor Imaging (Nugent et al., 2015).

One study examined the cortisol stress response among 32 patients with schizophrenia without a control group and observed a blunted stress response in a subgroup of patients (n=21) after the TSST (Tas et al., 2018).

Finally, a study by Steen et al. 2011 examined cortisol stress reactivity in patients with schizophrenia and bipolar disorder when compared to healthy participants (Steen et al., 2011). A significant group difference in percentage reduction of cortisol levels was found when healthy participants where compared to a combined schizophrenia/bipolar group. This difference disappeared when healthy participants were compared to either patients with schizophrenia or bipolar disorder separately, presumably because of the resulting lower sample sizes and power. The authors did not observe any significant differences in the cortisol stress response to the mental challenge task between patients with schizophrenia and bipolar disorder. In addition, significant negative associations were reported between reduced cortisol levels and increased number of psychotic episodes and depressive episodes when patients were considered as one psychosis patient group (Steen et al., 2011). We note that the used mental challenge task was a neuropsychological task under time pressure in front of the testers and two cortisol samples around the time of this task were collected.

4. Discussion

In this review, we focused on the cortisol stress reactivity in psychotic disorders across all illness stages, including the high-risk stage of psychosis after psychosocial stress. This is the first systematic review to show that there is a high degree of heterogeneity in study findings, which encompass all three illness stages - the high-risk stage, first-episode and the chronic stage – in psychosis. This finding is in line with the systematic review from Lange et al. 2017a for the first-episode and chronic stage of schizophrenia. Firstly, our general findings were that across the 17 studies reviewed, ten showed evidence of reduced cortisol levels (blunted response) following acute stress exposure. Secondly, when studies are sub-divided on the basis of illness and course, we observed reasonably consistent findings of blunted response in patients with chronic schizophrenia (seven of eight studies). The pattern of findings is more variable in individuals at high-risk of psychosis with two out of three studies reporting a blunted cortisol stress response. Two studies in patients with first-episode psychosis also observed reduced cortisol levels after the psychosocial stress task. Of note, however, many more studies of patients with chronic psychosis were available for inclusion in the study than for patients with either early stages of illness, or patients with bipolar disorder. We note that the high-risk state does not reflect a clinical diagnosis of psychosis. Typically, only a small percentage of individuals at the high-risk stage transition to psychosis in the following years.

Different factors for the variability of cortisol stress response to the psychosocial stressor or the lack of significant group differences have been discussed previously (Ciufolini et al., 2014, Lange et al., 2017a, Zorn et al., 2017), such as age, sex (Back et al., 2008, Allen et al., 2014), time of day and time of assessment (Dickerson and Kemeny, 2004), body mass index, status of menstrual cycle and use of contraception (Goldstein et al., 2015), lack of adherence to instructions for the cortisol sample collection, medication effect (in particular of antipsychotic

medication), different patient characteristics, variety of cortisol analysis techniques and publication bias of early studies (Ciufolini et al., 2014, Zorn et al., 2017, Lange et al., 2017a). It has also been proposed that a variety of different experimental paradigms of the psychosocial stress task may affect the variability of cortisol stress reactivity findings, for example, the majority of studies that used the TSST (both in the original or modified versions) found a reduced cortisol stress response, whereas the majority of studies that used an alternative but comparable psychosocial stress task observed no group differences (Lange et al., 2017a). Previous reviews only included TSST studies (Ciufolini et al., 2014, Zorn et al., 2017). However, in our review with a greater number of included studies than the previous systematic reviews, this potential effect of psychosocial stress task type seems to be irrelevant as the number of studies reporting no group differences versus reduced cortisol levels is balanced (i.e. No group difference: Two studies using the TSST versus three studies using an alternative stress task; Reduced cortisol levels: six studies using the TSST versus five studies using an alternative stress task).

In more recent years, studies used the analysis of the AUC as part of the Receiver Operating Characteristic (ROC) curve. This analysis allows researchers to consider inherent variability among data when, at this early stage of research, it is still unknown what constitutes defined threshold levels for presence or absence of a cortisol stress response to a psychosocial stress response in psychosis. Briefly, a ROC curve is defined as a graph plotting sensitivity and specificity in order to evaluate the quality or performance of a given test (Park et al., 2004). We found that five out of the 17 studies reported AUCi and AUCg as standardised cortisol outcome measures to interpret the influence of the psychosocial stress exposure on cortisol stress reactivity in contrast to the traditional statistical analyses of t-tests and χ^2-tests. Since 2015, five out of nine studies used this analysis (van Leeuwen et al., 2018, Lange et al., 2017b,

Brenner et al., 2011, Wieck et al., 2013, Seitz et al., 2019), which reflects the growing interest. We also observed another trend in the use of statistical analyses. Five out of 17 studies ran correlational post-hoc analyses between cortisol levels and outcome measures, such as psychotic symptom severity, depressive symptom severity, frequency and severity of early-life adversity during childhood, subjectively perceived stress around the time of the psychosocial stress task, subjectively perceived recent stress levels, cognitive function or brain imaging measures (van Leeuwen et al., 2018, Lange et al., 2017b, Nugent et al., 2015, Pruessner et al., 2013, Seitz et al., 2019). These findings may add to the interpretation of the cortisol levels despite the lack of causal interpretation.

Limitations of current studies

From a clinical perspective, there is a difficulty in interpreting correlations between cortisol levels and clinical outcome measures, such as severity of psychotic symptoms. This is the most commonly used outcome measure in psychosis research. However, the acute stress exposure during a psychosocial task is challenging to complete when patients suffer from current delusions, hallucinations and bizarre behaviour why the majority of included patients are clinically stable with relatively low symptom severity. Furthermore, the severity of psychotic symptoms varies considerably during the course of the illness and is therefore an unreliable outcome measure (Tohen et al., 2016). In addition, subjective coping strategies are known to be implicated in daily life functioning of patients with psychosis, such as psychosis as a stressful condition (Myin-Germeys et al., 2002). The role of recent stress in an individual's life (Allott et al., 2015, Reininghaus et al., 2016) has also been reported to impact on participant's coping in patients with psychosis and healthy participants alike when early-life adversity is existent. It is also relevant to consider the higher frequency and severity levels of early-life adversity seen in patients with psychosis as it has been reported that these patients have

increased hyperactivity of the HPA axis when compared to patients with no prior experience of childhood trauma (Braehler et al., 2005, Peng et al., 2014). These findings are in keeping in with significantly increased frequency of emotional abuse in patients with schizophrenia who were cortisol responders (Lange et al., 2017b).

Some future directions

While clinicians are often focused on variables associated with changes in clinical symptom severity, the last ten years has seen a growing appreciation of cognitive function as a more accurate predictor of social and occupational functioning (Green 2016). Deficits in cognitive function have a more stable course than clinical symptoms, often predating and then outlasting fluctuating symptoms. Variation in these deficits, which include the domains of general cognitive function, memory function, and social cognition, are associated with both genetic variation associated with psychosis risk (Blokland et al., 2017), and with exposure to early-life adversity (Dauvermann and Donohoe, 2019, Rokita et al., 2018). Although studies of the effects of changes in cortisol on cognitive performance following stress exposure are currently limited, the 'Immune Response and Social Cognition in Schizophrenia' ('iRELATE') project is an example of this direction. In this study, the influence of genetic markers, early-life adversity and both the immune and cortisol responses on cognition are examined in patients with schizophrenia and healthy controls. Specifically, we are testing the inter-relationships between the cortisol stress response following the TSST and performance on measures of higher cognitive function (for example, general cognitive ability, working memory and verbal memory) and social cognitive function (for example, emotion recognition and Theory of Mind). In particular, the social cognitive deficits are predictive of social and occupational function in schizophrenia (McGlade et al., 2008, Green, 2016, Green et al., 2012, Horan et al., 2012), bipolar disorder (Vlad et al., 2018) and psychosis (Lysaker et al., 2018). In addition,

social cognitive aspects may predict social functioning better than general cognitive ability (McGlade et al., 2008). Given the evidence that these deficits typically do not improve with antipsychotic treatment (Daros et al., 2014, Kucharska-Pietura and Mortimer, 2013), understanding the role of both HPA and immune responses to stress is pivotal to identifying targets for new treatments.

Conclusion

This review highlights recent evidence of blunting of cortisol response following experimentally-induced psychosocial stress across all stages of psychosis. While there was some evidence of this blunted response across illness types and stages, the strongest evidence was observed for those with chronic schizophrenia. Due to the low number of studies, in particular in bipolar disorder, much work is still needed to accurately characterise the biological effects of stress in psychosis.

Conflict of Interest statement

MRD and GD have no conflicts of interest to disclose.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this review was not required by their local Ethics Committee.

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Figure Legend

Figure 1. Flow diagram selection of study process

Table Legend

Table 1. Study characteristics and main findings