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Cortisol awakening response is decreased in patients with first-episode psychosis and increased in healthy controls with a history of severe childhood abuse

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ABSTRACT

Background: Childhood abuse is highly prevalent in psychosis patients, but whether/how it affects hypothalamic-pituitary-adrenal (HPA) axis at the onset of psychosis remains unclear. We aimed to investigate the effects of severity of childhood abuse on HPA axis activity, in first-episode psychosis (FEP) and healthy controls.
Methods: We recruited 169 FEP patients and 133 controls with different degrees of childhood physical and sexual abuse (i.e. no abuse exposure, non-severe abuse exposure, and severe abuse exposure). Saliva samples were collected to measure cortisol awakening response with respect to ground (CARg), increase (CARi) and diurnal (CDD) cortisol levels. Two-way ANOVA analyses were conducted to test the relationships between severity of childhood abuse and psychosis on cortisol levels in individuals with psychosis and healthy controls with and without childhood abuse history.
Results: A statistically significant interaction between childhood abuse and psychosis on CARg was found ($F_{(2,262)} = 4.60$, $p = 0.011$, $\omega^2 = 0.42$). Overall, controls showed a U-shaped relationship between abuse exposure and CARg, while patients showed an inverted U-shaped relationship. CARg values were markedly different between patients and controls with either no abuse history or exposure to severe childhood abuse. No significant differences were found when looking at CARi and CDD.
Conclusions: Our results show a divergent effect of severe childhood abuse on HPA axis activity in patients with first-episode psychosis and in controls. In the presence of exposure to severe childhood abuse, a blunted CARg and a less reactive HPA axis may represent one of the biological mechanisms involved in the development of psychosis.

1. Introduction

Individuals with psychosis report experiencing more frequent and more severe childhood abuse than people without past or current mental health conditions (Mauritz et al., 2013). Additionally childhood abuse has been associated with alterations in the stress response in adulthood, inducing changes in the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis that seem to partially mirror the biological abnormalities present in psychosis (Nemeroff and Binder, 2014; Wielaard et al., 2017). Clarifying which biological abnormalities in psychosis are specifically related to the experience of childhood abuse will improve our understanding of psychosis and may ultimately help to provide better and more personalised treatment.

When a situation is perceived as either physically or psychologically stressful, the orderly modulation of arousal and the selection of appropriate behavioural responses promotes adaptation to external demands; this is mostly obtained through the activation of the HPA axis and an increase in cortisol levels (Sandi and Haller, 2015). Indeed failure of coping with events that considerably challenge the capacity of the stress response system, such as childhood abuse, has been associated with changes in HPA axis activity and consequently altered behaviours in adulthood both in those with and without mental illnesses (Sandi and Haller, 2015). So far history of early abuse has magnified the

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alterations in cortisol production already associated with depression and PTSD, but comparatively little is known of its effect on HPA axis functioning in psychosis. In particular, while in individuals with depression, where a basal HPA axis hyperactivity is usually present, history of childhood maltreatment is associated with even higher basal cortisol levels. In patients with PTSD, where a basal hypoactivity of the HPA axis is usually reported, history of childhood maltreatment is associated with even lower basal cortisol levels (Tarullo and Gunnar, 2006; Strüber et al., 2014).

Likewise patients with psychosis and schizophrenia show abnormalities in HPA axis functioning. In particular individuals at their first episode as well as those with established psychosis show a specific pattern of cortisol abnormalities characterised by elevated diurnal cortisol levels (especially in individuals with no or minimal antipsychotic exposure), in combination with a blunted cortisol awakening response and reduced cortisol reactivity to social stressors (Borges et al., 2013; Ciufolini et al. 2014; Pruessner et al., 2017). In the context of individuals who are genetically, socially and/or psychologically vulnerable, early abuse may interact with an already susceptible HPA axis, determining maladaptive neurodevelopmental psychosis-relevant changes decisive for the developing of psychosis later in life (Walker and Diforio, 1997; Pruessner et al., 2017).

Notwithstanding the high prevalence of childhood abuse among individuals with psychosis, only four studies have investigated the effects of childhood abuse on cortisol levels in patients with psychosis with inconsistent results (Braehler et al., 2005; Mondelli et al., 2010; Borges et al., 2013; Ciufolini et al., 2014; Faravelli et al., 2017; Lange et al., 2017). While Braehler et al. (2005) found reduced cortisol production after awakening in individuals with schizophrenia and history of early abuse, in our previous work, we showed a correlation between childhood sexual abuse and increased cortisol awakening response in a sample of patients with first-episode psychosis (Mondelli et al., 2010). A result confirmed in a more recent study from Faravelli et al. (2017), where increased morning cortisol levels in psychotic patients with experience of childhood abuse were reported. Recently, childhood abuse has been associated with a reduced cortisol response to social stress in individuals with schizophrenia-spectrum disorders (Lange et al., 2017). Importantly, most of these studies included individuals with long-standing schizophrenia, making difficult to control for the potential impact of long-term antipsychotic treatment and chronicity of the illness; furthermore they investigated relatively small sized groups and tended to use a broad definition of abuse (Braehler et al., 2005; Mondelli et al., 2010; Faravelli et al., 2017; Lange et al., 2017). As different types and severities of early adversities are thought to have different biological consequences, collating individuals with different types (e.g. physical, emotional, neglect) and degree of abuse in the same sample may lead to the introduction of noise (Morgan et al., 2010; Varese et al., 2012). Physical and sexual abuse in childhood are associated with more severe consequences, in terms of poorer physical and mental health than other types of early abuse (e.g. neglect) and more consistent associations with HPA axis alterations (van der Vegt et al., 2009; Heim et al., 2008; Fogelman and Canli, 2018). Importantly, these associations are still present when controlling for the co-occurrence of other abusive experiences or socio-economic status (Heim et al., 2008; Green et al., 2010; Font and Maguire-Jack, 2015). Thus grouping individuals on the basis of exposure to physical and sexual abuse, along with information on the severity of these experiences, could identify a relatively more homogenous set of individuals, helping to characterise their stress response patterns.

Our study aims to investigate the effects of presence and degree of severity of childhood abuse on HPA axis activity in a sample of first-episode psychosis patients and healthy controls. We examined HPA axis activity by measuring both cortisol levels during the day and cortisol awakening response. We focussed specifically on childhood abuse before the age of 17; thus information on the severity of physical and sexual abusive experiences were recorded and participants were stratified according to that (we included 3 groups: history of no childhood abuse, history of non-severe childhood abuse, and history of severe childhood abuse). Finally, we recruited individuals at their first episode of psychosis in order to limit possible effects of long duration of illness and psychotropic medication.

Our primary hypothesis is that cortisol levels during the day and cortisol awakening response would be reduced in individuals with psychosis exposed to severe childhood abuse when compared with controls with the same history and degree of abuse. Furthermore, we hypothesised that there would be a progressive reduction in cortisol levels in relation to the severity of childhood abuse (i.e. individuals with severe childhood abuse will have a more pronounced cortisol reduction that those with history of non-severe abuse, and those with non-severe abuse would have lower cortisol levels than those not exposed to abuse) in patients as well as controls.

2. Methods

2.1. Subject recruitment

We recruited 169 first-episode psychosis patients (FEP) from the South London and Maudsley (SLaM) NHS Foundation Trust, London (UK), as part of the EU study on Gene-Environment Interactions in Psychosis (EUGEI), and the BRC Psychosis Theme study on Genetics and Psychosis (GAP). Recruitment procedures and assessments have been described in detail in previous papers (Habets et al., 2011; Mondelli et al., 2015). Patients diagnosed with a functional psychosis (ICD10 criteria; WHO, 1992) for a diagnosis of non-affective (F20–F29) and affective (F30–F33) psychosis, aged 18 to 65, who presented for the first time with a psychotic episode to the SLaM NHS Foundation Trust were recruited into the study (Di Forti et al., 2014; Mondelli et al., 2015). We recruited 133 healthy controls from the same catchment area. Controls were screened for any Axis I clinical disorders, any psychotic symptoms or any psychotic illness with the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995) and were excluded if they met criteria for a past or present psychotic disorder. Both patients and healthy controls were excluded if they had a history of any neurological disorder, loss of consciousness for >1 h and/or previous head trauma, learning disabilities, or lack of command of the English language.

2.2. Sample description

There was no significant difference in age between patients and controls ($t_{(166)} = 1.07$; $p = 0.31$). Patients were significantly more likely to be males and of non-white origin background than controls ($x^2_{(1)} = 6.5$, $p = 0.01$, and $x^2_{(5)} = 17$, $p < 0.02$, respectively). Conversely, controls had a significantly higher level of education and were more likely to be employed compared to patients ($x^2_{(3)} = 86$, $p < 0.001$, and $x^2_{(6)} = 88$, $p < 0.001$, respectively). The most common diagnosis was schizophrenia or schizophreniform disorder (53.5%), followed by bipolar disorder with psychotic features (12%), psychotic disorder not otherwise specified (12%), schizoaffective disorder (11.5%), major depressive disorder with psychotic features (9%) and delusional disorder (2%). All socio-demographic characteristics of the sample are reported in Table 1. Individuals with first-episode psychosis were more likely to have been exposed to moderate and severe abuse than healthy controls ($x^2_{(3)} = 15.84$, $p < 0.001$) (Table 1).

2.3. Evaluation of the abuse exposure

A semi-structured interview was used to elicit retrospective reports of childhood abuse occurring before 17 years of age using either the Childhood Experience of Care and Abuse interview or its later derived shortened version, the Childhood Experience of Care and Abuse Questionnaire (CECA-Q) (Bifulco et al., 1994; Bifulco et al., 2005). Information about loss or lack of care was collected for 30% of the sample

Table 1
Socio-demographic and clinical characteristics of the sample.

Socio-demographic characteristic cases	Cases (169)		Controls (133)			
	n	SD	n	SD		p value
Age (mean years)	28.1	7.59	26.9	8.23	$t_{(345)} = -1.07$	0.31
Female	59 (35%)		85 (64%)		$x^2 = 6.5$	0.01
Ethnicity (non-white origin)	109 (64%)		68 (51%)		$x^2 = 17$	0.02
Education (no qualifications)	29 (17%)		3 (2%)		$x^2 = 88$	<0.001
Employment (not employed)	68 (40%)		13 (9%)		$x^2 = 89$	<0.001

(17% of cases and 45% of controls). The present study focused only on physical and sexual abuse in childhood to have a relatively homogenous set of people with regard to their abusive experiences. A total of 58% of the participants were assessed using the CECA-Q and 42% with the CECA Interview. As items ascertaining the presence of physical and sexual abuse are essentially identical between the two scales, participants were coded on the basis of their abuse exposure irrespective of the instrument used to record it (Table 2).

Physical abuse was considered to be any event of violence towards the individual committed by an adult or older sibling in the household, which occurred before the age of 17 years.

Sexual abuse was defined as any unwanted sexual experience with an adult or peer (within or outside the family) that occurred before the age of 17 years. The final score for both physical and sexual abuse can range from 0 (no abuse) to 3 (severe abuse) (Bifulco et al., 2005). Cut-points published by Bifulco et al. (2005) were then used to dichotomize responses for physical and sexual abuse into severe and non-severe categories. Finally all participants in the study were assigned to one of the three groups according to the level of the severity of the most severe abuse experience ((0) neither physical nor sexual abuse, (1) non-severe physical and/or sexual abuse, (2) severe physical and/or sexual abuse). For example an individual with non-severe physical abuse and severe sexual abuse was included in the severe abuse group. Among the participants who reported abuse exposure, n = 34 participants (19.2%) experienced both physical and sexual abuse (this percentage was 23.6% among cases and 11.9% among controls).

2.4. Collection of saliva cortisol sample and measurement of cortisol levels

Participants collected saliva samples at awakening (0 min) and then at 15, 30, 60 min after awakening and again at 12:00 pm and 08:00 pm. Details of saliva collection and measures put in place to prevent sample contamination and artefacts have been reported previously (Mondelli et al., 2010). Cortisol levels were estimated using the High Sensitivity Salivary Cortisol ELISA KIT from Salimetrics, while in a small proportion of samples (36%) they were estimated using the "Immulite" DPPC's immunoassay analyser (www.diagnostic.siemens.com), as published before (Belvederi et al., 2012). Very high correlation was found between the values obtained with these different techniques (z-scores; r = 0.93; slope = 0.88; intercept = 1.38; standardized coefficient = 0.93; F = 15.1, p < 0.001). Standardized z-scores of cortisol measurements were used for statistical analyses as previously published (Mondelli et al., 2015). The basal activity of the HPA axis was measured as the cortisol during the day (CDD), calculated as the area under the curve with cortisol values at awakening and then at 12:00 pm and 08:00 pm. The spontaneous increase in cortisol concentration at awakening has been consistently used to evaluate the reactivity of the HPA axis (Clow et al. 2010). Any changes in the cortisol production within the first hour after awakening was measured as the area under the curve of salivary cortisol values at 0, 15, 30 and 60 min after awakening. Based on the formula used from Pruessner et al. (2003) we computed the CAR with respect to ground (CARg) and increase (CARi). CARg evaluates the total amount of cortisol present in the first hour after awakening, while CARi measures the variation (either positive or negative) in cortisol concentration within the first hour after awakening (Belvederi et al., 2012). CDD, CARg, and CARi met the normality assumptions after conversion to z-scores. Participants whose cortisol values were considered outliers (i.e. over two standard deviations from the mean) were excluded from the analyses, likewise those who had missing data. The final sample comprised 259 participants (123 controls and 136 patients) with data on CDD, 262 participants (124 controls and 138 patients) with data on CARg, and 258 participants (123 controls and 135 patients) with data on CARi.

Table 2
Childhood abuse distribution in the sample.

Childhood abuse	Cases (N = 169)	Controls (N = 133)	
	n (%)	n (%)	x^2 (df)
No abuse	59 (35)	66 (49)	21.3(2) p < 0.001
Non-severe abuse	61 (36)	49 (37)	
Severe abuse	49 (29)	18 (14)	

2.5. Assessment of medication exposure

Difference in cumulative antipsychotic exposure between individuals with and without a history of childhood abuse was calculated as total chlorpromazine-equivalent dose and compared across the different levels of abuse using independent samples *t*-test or one-way analysis of variance (ANOVA) as appropriate (Woods, 2003; Taylor et al., 2012). We found no difference in the levels of total antipsychotic exposure across the different severities of abuse ($x^2_{(3)} = 2.03$ p = 0.5), thus it was not included in the model.

2.6. Statistical analysis of abuse exposure and hypothalamic-pituitary-adrenal axis

A two-way ANOVA was used to estimate the effects of the exposure to physical and sexual abuse and psychosis on CDD, CARg and CARi. As the increase in severity of the level of abuse can signal the gradual rise in the magnitude of environmental stress (Suliman et al., 2009), we implemented a polynomial contrast to explore the best representation of the variations of CDD, CARg or CARi with the increase of abuse severity in the each of the ANOVA analyses performed.

3. Results

3.1. Effect of severity of childhood abuse and presence of psychosis on the hypothalamic-pituitary-adrenal axis

3.1.1. Cortisol awakening response with respect to the ground and childhood physical and sexual abuse

The two-way ANOVA looking at the effects of severity of childhood abuse and presence of psychosis on CARg in the entire sample was statistically significant ($F_{(5,262)} = 3.08$, p = 0.002). There was a statistically significant main effect of psychosis on CARg ($F_{(1,262)} = 11.90$, p < 0.001, $\omega^2 = 0.44$), with patients exhibiting an overall lower CARg than controls, irrespective of abuse exposure. There was a statistically significant interaction between the severity of childhood abuse and caseness on CARg ($F_{(2,262)} = 4.60$, p = 0.011, $\omega^2 = 0.42$). More specifically, there

was a U-shaped relationship between CARg and exposure to childhood abuse in controls, showing reduced CARg in controls with non-severe abuse exposure and increased CARg in those with a history of severe abuse when compared with those without such a history (Fig. 1). In contrast, patients showed an inverted U-shaped relationship between CARg and childhood abuse; in particular, patients with non-severe abuse had increased CARg and those with severe abuse a decreased CARg when compared with patients without an abuse history (Fig. 1). The observed overall power of the model was 99% explaining 14% of the variance in the data. When looking at effects of severity of childhood abuse, irrespective of the presence of psychosis, we found that subjects with history of severe physical and/or sexual abuse had lower CARg than both those with no abuse history or non-severe abuse in childhood, although this did not reach a statistically significant level ($F_{(2,262)} = 0.66$, $p = 0.5$, $\omega^2 = 0.10$).

3.1.2. Cortisol during the day and childhood physical and sexual abuse

The two-way ANOVA looking at the effects of severity of childhood abuse and presence of psychosis on cortisol levels during the day (CDD) was not statistically significant ($F_{(5, 259)} = 1.68$, $p = 0.1$).

3.1.3. Cortisol awakening response with respect to the increase and childhood physical and sexual abuse

The two-way ANOVA looking at the effects of severity of childhood abuse and presence of psychosis on Cortisol Awakening Response with respect to the increase (CARi) was not statistically significant ($F_{(5, 258)} = 1.63$, $p = 0.1$).

4. Discussion

We found divergent patterns between patients with first-episode psychosis and controls when looking at cortisol awakening response in relation to the severity of childhood abuse exposure. Our findings did not support a progressive reduction of cortisol levels and of HPA axis reactivity with increased severity of childhood abuse across patients and controls. In contrast, controls showed a U-shaped relationship between abuse exposure and cortisol awakening response (CARg), while patients showed an inverted U-shaped relationship. Importantly the CARg was markedly different between patients and controls with either no abuse history or exposure to severe childhood abuse, while patients and controls exposed to non-severe abuse had similar levels of CARg. Our results confirmed the hypothesis that patients exposed to severe childhood abuse present with reduced HPA axis reactivity (as shown by lower CARg) when compared with healthy controls exposed to severe childhood abuse. These findings confirmed our hypothesis that there would be a relationship between cortisol concentrations and the severity of the childhood abuse suffered. Interestingly, the direction of this relationship did not support our hypothesis that cortisol levels would be uniformly reduced in individuals with psychosis when compared to those of controls with the same abuse history. However irrespective of the presence of psychosis, there were no significant differences in diurnal cortisol levels or cortisol awakening response with respect to the increase between individuals with and without a history of childhood physical and/or sexual abuse in the entire sample.

For the first time, a divergent effect of abuse on cortisol awakening response contingent on the severity of abuse has been shown between patients with psychosis and healthy controls, pointing to a link between the exposure to childhood abuse and specific changes in HPA axis activity later on in life. Cortisol production is thought to be subordinate to the length and severity of the abuse; consistently, we found that different cortisol awakening responses are a function of different degrees of abuse (Raymond et al., 2017; van der Vegt et al., 2009). However, studies on overall adult populations report an inconsistent picture with reduced, high and unchanged cortisol concentrations and blunted as well as heightened reactivity (Bronsard et al., 2016; Raymond et al., 2017). This seems to be due to difficulties in separating out the confounding effect of underlying psychopathology and a tendency to group together different types and severity of abuse (Teicher et al., 2016). For example, we did not find an effect of childhood abuse on CARg when investigated irrespective of the presence of psychosis, probably because of the cases' and controls' specular CARg patterns. When taking into account psychosis, our results elegantly signal an intrinsic difference in the reactivity of the HPA axis, as CARg between cases and controls differed in the absence of childhood abuse ($t_{(117)} = 2.24$, $p = 0.02$), and this was magnified by the occurrence of severe childhood abuse ($t_{(52)} = 2.24$, $p = 0.003$). In the case of non-severe abuse, despite CARg being similar in cases and controls, this was the result of a different direction of change from CARg from the condition where childhood abuse was absent. This divergent effect shown by patients and controls may be the consequence of a combination of genetic predisposition and social characteristics/environment of individuals vulnerable to

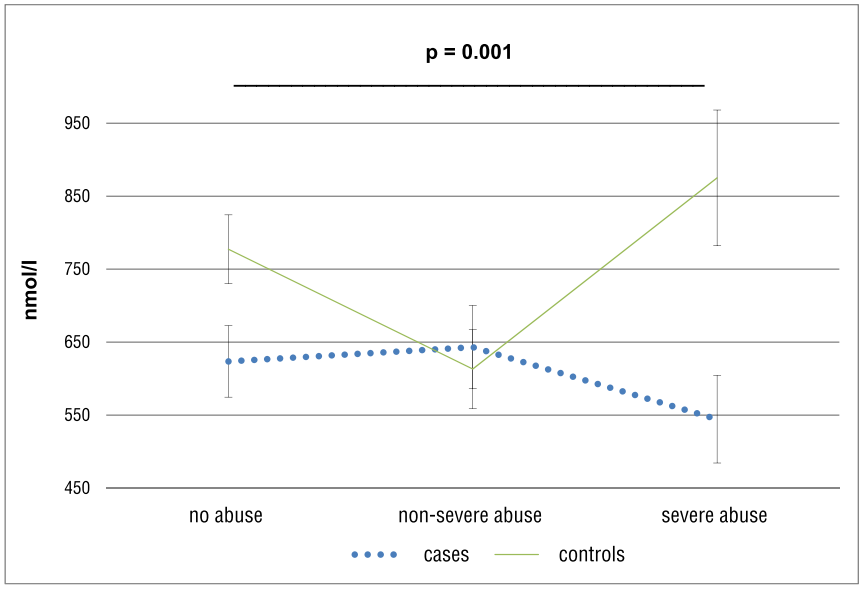

Fig. 1. Cortisol Awakening Response with respect to the ground; interaction between degrees of severity of abuse and psychosis ($F_{(2,262)} = 4.60$, $p = 0.001$, $\omega^2 = 0.42$); Error bars express the standard deviations.

psychosis which may impact the way the HPA axis modifies cortisol production in response to extreme stress (Miller et al., 2007; Morgan and Gayer-Anderson, 2016). For example in PTSD and depression, mutations of the FK506-binding protein (which modulates the activity of the glucocorticoid receptors) have been associated with increased risk of depression and PTSD in the presence of childhood abuse (Zannas et al., 2016; Halldorsdottir et al., 2017). Supporting this hypothesis, the increased risk of developing psychosis after exposure to early physical abuse in the AESOP study was lower among participants who had a large support network (Gayer-Anderson et al., 2015).

The possible lack of cortisol reactivity in psychosis is not a novel finding and has previously been reported in some, but not all studies (Mondelli et al., 2010; Ciufolini et al., 2014; Chaumette et al., 2016). As some studies did not report blunted cortisol at awakening in patients at their first episode of psychosis, our study provides possible explanations for these inconsistencies (Pruessner et al., 2008; Hempel et al., 2010; Pruessner et al., 2013; Girshkin et al., 2016). We found that patients with non-severe abuse exposure have comparatively higher CARg that those with no history of abuse, thus the lack of stratification for history of abuse exposure may lead to the grouping together of individuals with different CARgs, cancelling out differences.

In this context whether the low/blunted CARg should have positive or negative effects in patients with psychosis remains unclear. Indeed, lower levels of cortisol could protect from the toxicity associated with prolonged high levels of circulating glucocorticoids, proving adaptive in individuals whereby the toxic effect of cortisol could be amplified by the lack of protective mechanisms (Fries et al., 2005; Miller et al., 2007; Mondelli et al., 2010). For example, Brain-Derived Neurotrophic Factor (BDNF), a factor involved in neuronal development and cell survival in response to stress, has reported to be reduced in the presence of psychosis and concomitant childhood trauma and its lower levels contribute to smaller hippocampal volume in first-episode psychosis (Mondelli et al., 2011; Tomassi and Tosato, 2017). On the other side, the lack of an adequate cortisol response may also contribute to a more severe clinical picture. Indeed, cortisol suppresses inflammation directly and indirectly facilitates higher cognitive functions; individuals with psychosis show increased levels of inflammation and reduced CARg that has been associated with deficits in cognitive executive functions (Aas et al., 2011; Zajkowska and Mondelli, 2014). Importantly, we have previously reported than lower cortisol awakening response also predicts worse treatment response in first-episode psychosis, (Mondelli et al., 2015).

Somewhat surprisingly we did not find an effect of abuse on CARi nor did we find differences between patients and controls regarding this measure of cortisol concentration. CARi captures the variation (either positive or negative) of the cortisol concentration within the first hour after awakening, while CARg the total concentration in the same timeframe (Clow et al. 2010). CARi depends more than CARg on the starting levels of cortisol (first sample), therefore one possibility could be that the effect of abuse is more related to the overall concentration of cortisol at awakening rather than its variation. We also did not find an effect of abuse on CDD neither in cases nor controls. Studies on healthy populations describe an inconsistent picture of the association between childhood abuse and cortisol during the day. It is of note that studies with larger samples tend to report minimal or no effect of abuse and our results are consistent with this line of evidence (Bronsard et al., 2016; Raymond et al., 2017). However, we cannot completely exclude a possible effect of antipsychotic medication as indeed CDD tends to be normalized by those drugs more than CARg (Zhang et al., 2005; Popovic et al., 2007; Borges et al. 2013).

Some limitations and strengths of the study need to be acknowledged. First, the design of the study was cross-sectional and we evaluated retrospectively the exposure to childhood abuse. However, different measures were put in place to ensure the quality, accuracy and reliability of assessments. Importantly, the same interview as the one of this study was used in a sample of individuals with and without psychosis from South London with good levels of convergent validity with clinical case notes and patients' reports were stable over a 7-year period (Fisher et al., 2011). Second, our study focuses on the association between physical and sexual abuse and HPA axis activity without evaluating the possible co-occurrence of other types of traumatic experiences and this could be considered a limitation of the study. However, it has recently been shown that physical and sexual abuse are the most damaging types of early adverse experiences given they are associated with poorer physical health and more severe psychopathology when compared with other types of early adversities (Green et al., 2010). Furthermore, when tested in the same sample, abuse appeared to have an association with altered cortisol secretion of a greater magnitude than neglect (van der Vegt et al., 2009). Similarly, experiencing both physical and sexual abuse may increase their impact on the HPA axis. In order to estimate a potential confounding effect, we excluded these participants from a sensitivity analysis, which confirmed the significance our results. Third, the sample comprises a small minority of individuals with affective psychosis. Individuals with depression and childhood abuse report a heightened CAR and those with bipolar and a similar history of abuse show an inverted u-shaped effect. Unfortunately, it is still unclear whether and how the presence of psychosis in an affective condition may change what is known of the relationship between early abuse and HPA axis activity in pure affective conditions (Manenschijn et al., 2012; Tarullo and Gunnar, 2006; Strüber et al., 2014). This may have introduced a confounding effect which is difficult to control for in the current study. Finally, although strategies were put in place to monitor the quality of cortisol data (e.g. completion of collection sheet, refrigeration of samples, determination of saliva concentration), the collection of saliva was unsupervised hence it was not possible to detect erroneous reports of saliva collection time with potential consequences on the quality of the data. As the time of collection may have a greater impact on the estimation of the CARi rather than the CARg, this may have played a part in the lack of difference we found in CARi between patients and controls (Clow et al. 2010; Stalder et al., 2015).

A major strength of the study is the large sample of patients and controls; this is the largest study on which investigation of the effect of childhood trauma on cortisol levels in psychosis has been conducted. Furthermore, the study is very homogenous in terms of abuse exposure, as we focussed only on history of physical and sexual abuse, and a relatively large group of healthy individuals with a history of childhood abuse allowed, uniquely, to investigate resilience to traumatic experiences.

In conclusion, we showed that childhood abuse has a divergent effect on HPA axis activity in first-episode psychosis patients and in healthy controls dependent on the severity of abuse experienced. These findings provide an insight into the biological mechanisms present in individuals with psychosis exposed to different severities of childhood abuse, contributing towards a more nuanced understanding of the aetiology of psychosis and future development of more personalised treatment.

Contributors

Simone Ciufolini contributed to data analysis and interpretation and writing of the manuscript.

Charlotte Gayer Anderson, Helen L. Fisher, Tiago Reis Marques, Heather Taylor and Marta Di Forti contributed to the recruitment of the subjects, collection of the data and interpretation of the data. Patricia Zunszain contributed with analyses of salivary cortisol. Craig Morgan, Robin M. Murray, Carmine M. Pariante and Paola Dazzan contributed to data analysis and interpretation, and writing of the manuscript. Valeria Mondelli contributed to study design, recruitment of the subjects, data collection, analysis and interpretation, and writing of the manuscript.

Conflict of interest

The authors do not have any conflict of interest to disclose.

Role of funding sources

The funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

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