Association Between Self-Reported Childhood Maltreatment and Cortisol Profiles in Psychotic Patients

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February 2008

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the Masters of Science (M.Sc.)

Your file Votre référence
ISBN: 978-0-494-51351-4
Our file Notre référence
ISBN: 978-0-494-51351-4

ACKNOWLEDGMENT

I would like to thank several people for their support throughout the course of my thesis. First, I would like to thank Dr. Suzanne King for providing me with this opportunity, and for her guidance throughout the course of my research. I would like to thank my parents for their constant presence and support. I would also like to thank the many colleagues who directly or indirectly help me get all the way through. Christine Braehler, Dominique Saheb, Karène Brenner, Isabelle Marceau and David Laplante deserve special mentions for their continuous support over the years. I would lastly like to thank Serge Charlebois for his assistance and the many laughs he provided along the way.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

PTSD	Post traumatic stress disorder
HPA	Hypothalamic –Pituitary-Adrenal
PVN	Paraventricular nucleus
CRH	Corticotrophin hormone
AVP	Argine vasopressin
ACTH	Adrenocorticotropic hormone
AUC	Area under the curve
AUC_i	Area under the curve increase
AUC_g	Area under the curve ground
CTQ	Childhood Trauma Questionnaire
SCID	Structured Clinician Interview for DSM-IV
DSM	Diagnostic Statistical Manual
BPRS	Brief Psychiatric Rating Scale
TSST	Trier Social Stress Test
PANSS	Positive and Negative Syndrome Scale

ABSTRACT

Childhood maltreatment is extremely common in patients diagnosed with psychotic disorders. Moreover, it has been linked with impaired functioning of the Hypothalamic-Pituitary-Adrenal axis. Furthermore, abnormality of the HPA has been found in psychotic patients. Presence of childhood maltreatment could then explain why the HPA axis is dysfunctional in these subjects. Our objective was to clarify the role of childhood trauma in the cortisol profiles of psychotic patients. Thirty-one patients underwent assessments of childhood maltreatment. Diurnal cortisol and cortisol after a controlled psychosocial stress were also collected. Our results show that childhood trauma is associated with lower cortisol levels during the morning and during 24 hours. In men diagnosed with psychosis, childhood trauma is also associated with a higher cortisol response during psychosocial stress. This suggests an alteration of the HPA axis in psychotic patients, resulting from early trauma. Moreover, our results suggest that looking at specific types of childhood abuse may also be important.

RÉSUMÉ

Les maltraitement durant l'enfance sont extrêmement communs chez les patients psychotiques. De plus, ils sont liés au fonctionnement anormal de l'axe corticotrope. Par ailleurs, un dysfonctionnement de l'axe corticotrope fut démontré chez les patients psychotiques. Ainsi, la présence de traumatismes durant l'enfance pourrait expliquer pourquoi l'axe corticotrope des patients psychotiques est anormal. Notre objectif fut de clarifier le rôle des traumatismes de l'enfance sur le profil du cortisol des patients psychotiques. Nous avons collecté des données sur les traumatismes de l'enfance, le cortisol diurne, ainsi que le cortisol lors d'un stress psychosocial pour 31 patients. Nos résultats démontrent que les traumatismes de l'enfance sont associés à un niveau moins élevé de cortisol le matin ainsi que durant 24 heures. Chez les hommes avec un diagnostique de trouble psychotique, les traumatismes de l'enfance sont associés à une plus grande réponse de cortisol durant le stress psychosocial. Ceci suggère une altération du fonctionnement de l'axe corticotrope chez les patients psychotiques, due aux traumatismes de l'enfance. De plus, nos résultats suggèrent qu'il peut être important de prendre en compte les types spécifiques d'abus lors de l'enfance.

INTRODUCTION

Psychosis refers to a mental state involving a loss of contact with reality, which can be expressed in symptoms such as hallucinations, delusions, thought disorder and lack of insight. Today, the most prevalent causal model for this disorder is the diathesis-stress model (Walker & Diforio, 1997). This biopsychosocial model stipulates that a constitutional vulnerability exists in patients with psychotic disorders. Within this paradigm, the diathesis is believed to be genetically determined, with a possible impact of early environmental risk factors, such as obstetric complications. The vulnerability is associated with heightened sensitivity to stressors, so that later stress in life can precipitate the onset of the illness. The model proposed by Walker and Diforio identifies the vulnerability as being an abnormality in the dopaminergic system, which is later influenced by stress exposure via the stress hormone, cortisol. In this model, later stress in life raises cortisol levels, which exacerbates the constitutional abnormalities, resulting in the onset of the illness.

Recently, Read and colleagues, expanded the diathesis-stress model by proposing the traumagenic model (J. Read, Perry, Moskowitz, & Connolly, 2001). The traumagenic model stipulates that the neurological and biochemical constitutional vulnerabilities found in psychosis may also be caused by the long lasting consequences of childhood abuse and neglect on cortisol regulation. By reviewing studies on the abnormalities caused by childhood trauma, Read and colleagues show that a better understanding of the effects of trauma on the oversensitivity to stress found in patients with psychotic disorders could help in the understanding of the pathways that lead to positive and negative symptoms.

In the present work, we will review how childhood trauma is indeed extremely prevalent in patients with psychotic disorders. We will also review how childhood trauma may impact the proper functioning of the cortisol system, and how this system is abnormal in psychotic patients. Given the high rate of childhood trauma in psychosis, and the known impact of trauma on the cortisol system, we propose that childhood trauma may explain variance in both diurnal and reactive cortisol in psychotic patients; this has never been adequately tested. Our objective was to clarify the role of self-reported childhood trauma in the diurnal salivary

cortisol and reactive salivary cortisol profiles of psychotic patients. To accomplish this, we collected diurnal cortisol samples in chronic patients; we also collected cortisol samples before and after a controlled psychosocial stress in samples of chronic schizophrenic patients and associated these data with the self-reported severity of childhood maltreatment.

LITERATURE REVIEW

Childhood trauma

Traumatic experiences result from events threatening one's life or one's integrity, leaving the victim with a sense of helplessness, fear and horror. In extreme cases, traumatic experiences can lead to post-traumatic stress disorder (PTSD), which symptoms include: repeatedly reexperiencing the traumatic experience, hyperarousal, emotional numbing and avoidance of the stimuli reminiscent of the traumatic experience. Traumatic experiences are derived from situations of abuse and neglect.

Studies have shown that there is a greater prevalence of self-reported abuse and neglect in populations with severe mental illness than in the general population. While it could be argued that self-reported exposure to trauma in severe mental illness is neither valid nor reliable, studies with that population have found a Kappa coefficient of .63 for physical abuse and of .82 for sexual abuse (Meyer, Muenzenmaier, Cancienne, & Struening, 1996), suggesting good to very good reliability. Moreover, cross-validations between patient reports and independent clinical assessments of childhood trauma (i.e. chart reviews) range from 75% to 82% (Meyer et al., 1996; J. Read, Agar, Argyle, & Aderhold, 2003). These studies found that, if anything, psychotic patients tend to underreport abuse (John Read, 1997).

While general population studies find lifetime trauma exposure prevalence rates of 56% (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), abuse in severe mental illness is extremely common, with up to 98% of patients reporting at least one traumatic event in their lifetime (Mueser et al., 1998). Studies looking at childhood sexual abuse in populations with psychotic disorders have also found very significant results. For example, it has been found that up to two thirds of women and up to one third of men with psychotic disorders report having been sexually abused during childhood (Goodman, Rosenberg, Mueser, & Drake, 1997), compared to 30% for

women and 14% for men in the general population (Briere & Elliott, 2003). In a first episode sample, 68% of the sample reported trauma exposure, and 49% qualified the trauma exposure as "life-threatening" (Neria, Bromet, Sievers, Lavelle, & Fochtmann, 2002). Furthermore, a recent study concluded that subjects with a probable or definite diagnosis of psychosis were 15 times more likely to have been sexually abused during their childhood (Bebbington et al., 2004).

As mentioned, rates of childhood sexual abuse are higher in patients with psychotic disorders compared to normal controls. This is also true for rates of childhood physical abuse. A review of 39 studies concluded that 48% of female inpatients reported having been physically abused during childhood (J. Read et al., 2005), compared to 19% of women in the general population (Briere & Elliott, 2003). Two other studies using similar methodology found that 29% of female and 17% of male inpatients diagnosed with psychosis reported childhood physical abuse (Neria et al., 2002), for only 5% in the general population (Kessler et al., 1995). Moreover, up to 60% of female and 36% of male inpatients diagnosed with psychosis report childhood history of both physical and sexual abuse (J. Read et al., 2005).

The consequences of the high rates of childhood abuse cannot be underestimated. Indeed, positive correlations between level of abuse and level of psychopathology have been found in clinical (Lange, Kooiman, Huberts, & van Oostendorp, 1995) and non clinical (Mullen, Martin, Anderson, Romans, & Herbison, 1993) samples. Furthermore, in patients with psychosis, a history of childhood abuse and neglect is linked to a higher need for seclusion when hospitalized (Beck & van der Kolk, 1987), an earlier age of onset (Goff, Brotman, Kindlon, Waites, & Amico, 1991), longer hospitalizations, and higher risk of suicide (J. Read, 1998). Experiencing multiple types of trauma and neglect during childhood increases the chances of reporting hallucinations during adulthood (Shevlin, Dorahy, & Adamson, 2007). Furthermore, patients with hallucinations are 5 times more likely to have been both physically and sexually abused during their childhood compared to patients not reporting hallucinations (Whitfield, Dube, Felitti, & Anda, 2005). Moreover, severity of childhood maltreatment is associated with the frequency and severity of hallucinations and delusions (Schenkel et al., 2005).

Similar results are also found in the population at large. In general, higher levels of childhood trauma are associated with higher levels of psychotic symptoms, even in the general population (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006). Healthy controls having experienced childhood abuse of mild severity are twice more likely than non-abused controls to experience psychotic symptoms; controls with moderate and high severity of abuse are respectively 10.6 and 48.4 times more likely to have similar psychotic experiences (Janssen et al., 2004).

Hypothalamic-Pituitary-Adrenal axis and Cortisol

The high prevalence of childhood trauma in severe mental illness is important since it has been shown that psychosocial stress readily activates the HPA axis via release of the stress hormone cortisol (C. Kirschbaum, Pirke, & Hellhammer, 1993). However, not all psychosocial stress seems to elicit a significant cortisol response. A recent meta-analyis concluded that two important characteristics of the stressful situation must be present to elicit such a response: self-evaluative threat and uncontrollability (Dickerson & Kemeny, 2004). Self-evaluative threats are present when valued characteristics (e.g. intelligence) are threatened to be negatively evaluated by others, and are linked to shame or a potential loss of self-esteem. Uncontrollability refers to situations in which the context irrevocably leads to failure, or when negative consequences are unavoidable. Studies have shown that each characteristic alone produces a significant cortisol increase. However, the presence of both variables at the same time acts in synergy in producing the greatest cortisol responses (Dickerson & Kemeny, 2004). Since traumatic experiences can readily be conceptualized as threats to the self and as unavoidable, especially during childhood, they fall well within the experiences eliciting the most significant cortisol increases.

The cortisol increase observed following a threat experience occurs within the context of a complex biological system. As stated earlier, cortisol is the stress hormone produced by the activation of the HPA axis in humans. Following a psychosocial stress, or a traumatic experience, cognitive appraisal of the stressful environmental stimulus can lead to activation of the limbic system via its connections to the prefrontal cortex. The limbic system, especially the hippocampus, can then stimulate the HPA axis. Specifically, when limbic brain structures perceive threat to

homeostasis, the paraventricular nucleus (PVN) of the hypothalamus releases a corticotrophin-releasing hormone (CRH) and argine vasopressin (AVP) in the hypophyseal portal circulation; CRH and AVP then synergically stimulate the anterior pituitary, which releases pulses of adrenocorticotropic hormone (ACTH) and endorphins into the systemic circulation; ACTH then stimulates the adrenal cortex to synthesize and secrete cortisol. Cortisol in turns triggers a negative feedback loop that directly decreases the production of CRH and ACTH. In addition to its negative feedback at the level of the hypothalamus and the pituitary gland, activation by cortisol of glucocorticoid receptors on the hippocampus inhibits the HPA axis by reducing the release of CRH.

In normal subjects, cortisol follows a distinctive circadian rhythm, with cortisol levels being at their lowest around midnight. The hormone levels then rise until the awakening response occurs: cortisol increases between waking and 30 minutes later, then declines again in the subsequent 30 minutes. A gradual decline then follows during the day (Buckley & Schatzberg, 2005). This diurnal rhythm repeats itself day after day. Cortisol is an important hormone in humans, mobilizing energy for the body via elevation of glucose levels; it also serves as a regulating hormone, by inhibiting certain aspects of the immune system, and facilitating the effects of catecholamine on the cardiovascular system, for example (Dickerson & Kemeny, 2004).

Research on cortisol is done via plasma, urinary or salivary cortisol sampling. While these sampling methods are highly correlated (C. Kirschbaum & Hellhammer, 1994), salivary sampling is often preferred for its low cost, its non-invasiveness, and the fact that it can easily be conducted outside of the laboratory. However, since salivary sampling is frequently done outside of a controlled setting, it often leads to poor compliance and some deviation from strict research protocols (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007).

Cortisol studies use different research paradigms, depending on the aims of the study. For example, total 24h-integrated cortisol secretions is used to study diurnal cortisol levels across conditions. However, it is often of interest to look at the cortisol response over time. To conduct such an analysis, one can look at pre- and

post-event levels of cortisol, or use repeated measures of analyses of variance. Moreover, new methods of analysis have been developed, using the information contained in the area under the curve (AUC), being an estimate of total cortisol secretion within a given time period (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Two main AUC approaches have been proposed. The first method is the AUC with respect to increase (AUC_i), which calculates the AUC in accordance with variations from the first measurement. AUC_i can hence be interpreted as a measure of the "sensitivity of the system", being more sensitive to changes over time. The second method is the AUC with respect to ground (AUC_g), which calculates the total AUC under each measurement at each time point. The AUC_g is interpreted mostly as being the "total hormonal output" produced during the time period of interest (Pruessner et al., 2003). Integrated cortisol, which is used to calculate cortisol secretion over a specific time period, is simply measured by dividing the AUC_g by the time period of interest, and results in a measure of secretion/time.

Both AUC methods are routinely used to study the "waking response" and cortisol in reaction to other events. The waking response refers to the cortisol response in the first 60 minutes following awakening. While the exact putative role of the waking response is still under research, it has been shown to be influenced by variables such as gender, smoking habits, effect of lighting conditions and the day of the week, although results are not consistent across studies (for a review, see Clow, Thorn, Evans, & Hucklebridge, 2004).

Reactive cortisol refers to the change in cortisol levels following some stress imposed on the organism, other than waking. The stress can be either metabolic or psychosocial. Reactive cortisol following psychosocial stress has been shown to be influenced by a host of variables. For example, it was found that there is a greater reactivity in males compared to females following public speaking, mental arithmetic (Collins & Frankenhaeuser, 1978; C. Kirschbaum, Wust, & Hellhammer, 1992) and following a cognitive task (Collins & Frankenhaeuser, 1978), but that there is a greater reactivity in females following social rejection (Stroud, Salovey, & Epel, 2002). However, recent reports suggest no gender differences (Kudielka, Buske-

Kirschbaum, Hellhammer, & Kirschbaum, 2004). These conflicting results are probably due to an interaction between age and gender, since it was shown that older subjects show greater responses, especially in women (Otte, Hart et al., 2005; Seeman, Singer, & Charpentier, 1995). Greater reactivity in response to psychosocial stress is indeed found in younger men and older women (Seeman, Singer, Wilkinson, & McEwen, 2001).

Other variables affecting the cortisol response to a psychosocial stress are smoking (C. Kirschbaum, Scherer, & Strasburger, 1994; C. Kirschbaum, Strasburger, & Langkrar, 1993; Pickworth & Fant, 1998), with smokers having lower cortisol reactivity, and mental health status. Effectively, major depressive disorder is characterized by higher diurnal cortisol, or hypercortisolism (Michelson & Gold, 1998), and depressed patients show a blunted cortisol response to standard psychosocial stress (Burke, Davis, Otte, & Mohr, 2005). Moreover, patients with a diagnosis of post-traumatic stress disorder show lower diurnal cortisol, or hypocortisolism (Olff, Guzelcan, de Vries, Assies, & Gersons, 2006), and have a higher cortisol response to psychosocial stress (Bremner, Vythilingam, Vermetten et al., 2003; Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003).

Cortisol and childhood trauma

Repeated trauma during childhood has been shown to have dire consequences on the developing HPA axis. Indeed, after repeated exposure to cortisol, key structures of the axis, like the pituitary gland (C. Heim et al., 2000) and the hippocampus (Starkman, Gebarski, Berent, & Schteingart, 1992), have been found to be structurally damaged, thus compromising the normal functioning of the axis (Sapolsky, Uno, Rebert, & Finch, 1990). This is evidenced in studies of child victims of extreme neglect, who present increased levels of total daily cortisol compared to control children (Gunnar, Morison, Chisholm, & Schuder, 2001); however, sexually abused girls do not necessarily show different levels of 24-h urinary cortisol compared to non-sexually abused girls (De Bellis et al., 1994). Moreover, there are some indications that, when compared to children who are victims of only one type of maltreatment, children who are victims of both physical and sexual abuse show higher morning cortisol (Cicchetti & Rogosch, 2001a); however, when children who

are victims of only one type of trauma, be it sexual (J. A. King, Mandansky, King, Fletcher, & Brewer, 2001) or physical (Cicchetti & Rogosch, 2001b), are compared to non-maltreated children, studies have found lower morning levels among victims.

One possible confounding variable explaining these different results is the presence of comorbid psychopathology. Indeed, compared to non-depressed maltreated children, depressed children with childhood trauma show lower morning cortisol concentrations and are more likely to show a rise instead of a decline in cortisol during the day (Hart, Gunnar, & Cicchetti, 1996). Furthermore, there is evidence that there is lower cortisol reactivity in maltreated preschoolers (Hart, Gunnar, & Cicchetti, 1995).

Studies of adults survivors of trauma also demonstrate altered HPA axis functioning. For instance, subjects maltreated during childhood present lower baseline cortisol (C. Heim, Newport, Bonsall, Miller, & Nemeroff, 2001) and greater amount of morning cortisol (Weissbecker, Floyd, Dedert, Salmon, & Sephton, 2005). Moreover, it was found that adults maltreated during childhood show higher cortisol response to a stressful video (Luecken, 1998), although at least one study did not arrive at such results (Otte, Neylan et al., 2005). Again, one possible confounding variable in these studies is the presence of psychopathology: adults with both early parental loss and current psychiatric disorder have higher levels of diurnal cortisol compared to adults with early parental loss and no psychiatric disorder (Breier, 1989). Women having experienced childhood abuse and PTSD related to the abuse also have higher cortisol levels compared to women with childhood abuse experience but no PTSD, and to women who have not been abused (Bremner, Vythilingam, Vermetten et al., 2003; Lemieux & Coe, 1995). Furthermore, abused women with depression have a higher response to stress when compared to abused women without depression and non-abused women (C. Heim et al., 2000). Finally, abused women with PTSD have elevated cortisol response to abuse scripts compared to women without PTSD (Elzinga et al., 2003). It is hence possible that childhood trauma and presence of psychopathology interact to explain variations in the HPA axis of adult survivors of trauma.

Cortisol and psychosis

HPA axis dysregulation has also been found in populations of psychotic patients. It may be argued that cortisol dysregulation in psychosis is due, in part, to neuroleptic treatment, since antipsychotics have been shown to have an impact on the HPA axis by decreasing diurnal cortisol levels (Meltzer, 1989; Rybakowski & Linka, 1991; Scheepers, Gespen de Wied, & Kahn, 2001; Wik, 1995). However, other studies have indicated that long term and chronic use of neuroleptic treatment has no impact on cortisol levels (Kaneda, Fujii, & Ohmori, 2002; Meador-Woodruff & Greden, 1988). It is of note that, to our knowledge, no studies to date have explored the impact of neuroleptic medication on cortisol response following psychosocial stress. While some studies have looked at the impact of neuroleptic medication on metabolic stress, review of this research is beyond the scope of the current review.

Another argument against the possible implication of neuroleptic medication as the cause of cortisol dysregulation in psychosis is that diurnal cortisol levels are found to be higher, not lower, in patients than in controls (Albus, Ackenheil, Engel, & Muller, 1982; Copolov et al., 1989; Franzen, 1971; Gallagher, Watson, Smith, Young, & Ferrier, 2007; Muck-Seler, Pivac, Jakovljevic, & Brzovic, 1999). Patients with a first psychotic episode who never took antipsychotic medication also show higher levels of cortisol compared to controls (Ryan, Sharifi, Condren, & Thakore, 2004; Walsh, Spelman, Sharifi, & Thakore, 2005). However, other studies did not find any differences in diurnal cortisol levels between medicated subjects and healthy controls (Jansen, Gispen-de Wied, & Kahn, 2000; Ritsner et al., 2004), or between drug-naïve psychotic patients, chronic patients and healthy controls (Rao et al., 1995). It is possible that the differences in these results are confounded by the presence of childhood trauma in some patients; a recent report from our group concluded that the presence of one or more types of moderate childhood trauma was significantly associated with lower morning cortisol in schizophrenic patients compared to non-maltreated patients, and that the impact of childhood trauma on 24-h integrated cortisol was also close to being significantly lower in the trauma group compared to the non-trauma group (Braehler et al., 2005). It is hence possible that basal cortisol in psychosis is affected by the pathology itself, elevating the basal cortisol levels; and by the presence of childhood trauma which would lower basal cortisol levels.

Sensitivity to stress seems to also be compromised in patients with psychosis. After a surgical stress, patients have a blunted cortisol response compared to healthy controls (Kudoh, Kudo, Ishihara, & Matsuki, 1997) – similar results were found after a cold pressor test, white noise, and a lumbar puncture (Albus et al., 1982; Breier, Wolkowitz, Doran, Bellar, & Pickar, 1988). Psychotic patients also show a blunted cortisol response following a psychosocial stress (Jansen et al., 1998; Jansen et al., 2000). This is interesting in light of the vulnerability-stress model of psychosis, which posits that psychosis is linked to a heightened sensitivity to stressors, and hence predicted a higher, rather than blunted, cortisol response.

PROBLEM STATEMENT AND OBJECTIVES

There are inconsistencies in the literature regarding the diurnal cortisol profile in psychosis, and reactive cortisol has been found to be blunted in that population. Given the high rate of trauma in psychosis, and the known impact of trauma on the HPA axis, childhood trauma may explain much of the variance in diurnal, morning and reactive cortisol in psychotic patients; this, however, has never been adequately tested. In addition, there is evidence that childhood trauma and depressive symptoms interact in predicting reactive cortisol from a psychosocial stress – this has never been explored in a population of psychotic patients. Hence, the objectives of this study were to:

1- Clarify the role of self-reported childhood trauma in the basal salivary cortisol profile and reactive salivary cortisol of psychotic patients;

2- Determine the extent to which depression may interact with childhood trauma in explaining basal salivary cortisol and reactive salivary cortisol in psychosis.

In general, we planned to test the association between childhood trauma and cortisol in psychosis, controlling for age, sex and depression. We also planned to explore the interaction between childhood trauma and depression on cortisol in psychotic disorders, controlling for the same variables. More specifically, we planned to answer these four research questions:

Research Question 1: Basal Cortisol

A- Controlling for age, sex and depression, what is the association between self-reported childhood trauma and basal salivary cortisol - secretion (i) in the morning and (ii) over a 24h period?

B- Do childhood trauma and depression interact to explain variance in basal cortisol - secretion (i) in the morning and (ii) over a 24h period?

Research Question 2: Reactive Cortisol

A- Controlling for age, sex and depression, what is the association between self-reported childhood trauma and salivary cortisol reaction in response to a psychosocial stressor?

B- Do childhood trauma and depression interact to explain variance in cortisol reaction in response to a psychosocial stress?

METHOD

Subjects

Thirty-one chronic patients, ill for at least 2 years, accepted to participate in the study. Patients were diagnosed with a psychotic disorder, and were stabilized. They spoke either French or English, and were able to provide informed consent. Patients over 40 and younger than 18 years old were excluded from this study, as well as patients with a past or current PTSD diagnosis.

Because complete data were not obtained for all subjects, sample sizes vary depending on the research question.

Research question 1 – Childhood trauma and basal cortisol:

Diurnal and morning cortisol were collected on 24 chronic patients.

Research question 2 – Childhood trauma and reactive cortisol

Reactive cortisol was collected on 23 chronic patients.

Instruments

Diagnosis

Presence of a diagnosis of psychotic disorder was confirmed with the use of the Structured Clinical Interview for the DSM-IV (SCID-I) (First, Spitzer, Gibbon, & Williams, 1995). The SCID is a semi-structured interview allowing to establish a diagnosis on the Axis 1 of the DSM-IV; modules for psychotic, mood, substance and anxiety disorders were used in the current study. To ensure maximum reliability for

diagnosis, interviewers underwent an intensive training schedule including watching 10 hours of training tapes, doing mock interviews with confederates, and doing practice interviews with trained interviewers.

Childhood Trauma

The Childhood Trauma Questionnaire (CTQ) (Bernstein, 1998) was used to assess trauma exposure and severity. The CTQ is a 34-item self report questionnaire that contains 5 subscales of 5 items each: Emotional Abuse, Sexual Abuse, Physical Abuse, Emotional Neglect, and Physical Neglect; the remaining items (9) are used to calculate a minimization score. Individual items are on a 5-point Likert scale ranging from "never true"(0) to "very often true" (5). Composite scores are calculated by summing up the relevant scores for each subscale. Composite scores can also be calculated by summing up the scores of different subscales to create the total score, the total abuse score, and the total neglect score. Cronbach's alpha for the CTQ ranges from .79 to .94, with a test-retest correlation of .88 (Fink, 1995).

In light of the literature review, it was presented that both abuse and neglect could have detrimental effects on the developing HPA axis. We hence used the total trauma score of the CTQ for our primary analyses, calculated by summing all the CTQ subscales.

Symptom Severity

The severity of the patients' symptoms was evaluated via the 24-item expended Brief Psychiatric Rating Scale (BPRS) (Ventura, Lukoff et al., 1993). The BPRS is a structured clinical interview covering the severity and frequency of 24 symptoms over the past month. Rating for each symptom goes from absent (1) to severe (7) on a 7-point Likert scale. The BPRS yields 4 factors: Negative Symptoms (3 items), Positive Symptoms (6 items), Excitement (6 items) and Dysphoria (4 items) (Ventura, Nuechterlein, Subotnik, & Gilbert, 1995). In inter-rater reliability studies, intra-class correlation for the BPRS ranges from .85 to .88 (Ventura, Green, Shaner, & Liberman, 1993).

In the analyses, we used the Dysphoria subscale – which contains the items for depression, anxiety, guilt and suicidality – the Dysphoria subscale has a Cronbach's alpha of .75 (Dingemans, 1990).

Cortisol measures

Salivary free cortisol concentrations were measured (μg/dl) by specific radioimmunoassay.

Diurnal and Morning Cortisol. Subjects were given 7 salivettes and were instructed to take saliva samples at 7 time points during the day: awakening, awakening +30 minutes, awakening +60 minutes, before lunch, 3 hours after lunch, at bed time, and at awakening the following day. While diurnal cortisol was measured using all 7 samples, morning cortisol was measured by using only the first 3: awakening, awakening +30 minutes and awakening +60 minutes. Subjects were asked to refrain from eating, drinking, brushing their teeth, smoking and doing physical exercise for one hour and a half before saliva sampling since this could have had an impact on their level of cortisol.

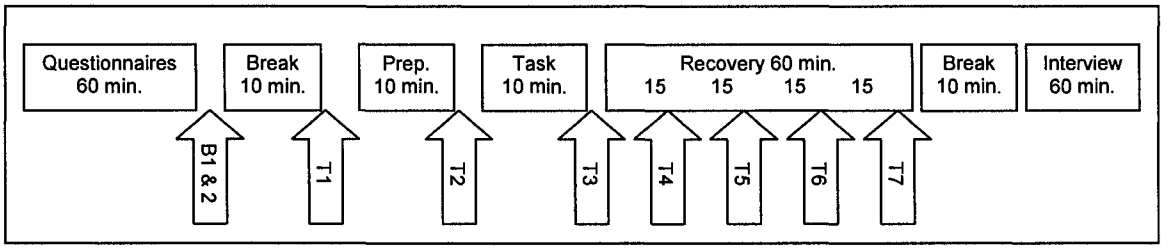
Reactive Cortisol: Trier Social Stress Test (TSST). The reactivity to psychosocial stress was measured by the Trier Social Stress Test (TSST), which has been shown to increase cortisol levels in normal subjects significantly, (C. Kirschbaum, Pirke et al., 1993; McRae et al., 2006). This test involves free speech and mental arithmetic in front of an audience. TSST sessions are done between 1 pm and 4 pm since levels of cortisol are relatively low during that time, which allows changes in cortisol concentrations to be more easily observed. The subjects are first instructed to prepare a speech during the next 10 minutes (anticipatory phase), after which they have to present the speech in front of the experimenter and a one-way mirror behind which the subjects are led to believe that evaluators are observing (production phase). The speech lasts 5 minutes, after which the subjects have to perform mental arithmetic during 5 more minutes, always in front of the experimenter and the one-way mirror. Saliva samples are collected during both phases of the test at 8 different time points (see Figure 1). Subjects were asked to refrain from eating, drinking, brushing their teeth, smoking and doing physical exercises one hour and a half before the saliva sampling, since this could have had an impact on their level of cortisol.

Area Under the Curve (AUC). For the purpose of this study, cortisol analysis was done via the Area Under the Curve methodology. Again, while AUC_i is a

measure of the sensitivity of the system, and is calculated in accordance with variation from the first measurement; AUC_g is a measure of the total area under the curve under each measurement for each time point, and is hence a measure of the total hormonal output. The formulae used for the calculations were taken from the article by Pruessner and colleagues (Pruessner et al., 2003):

Figure 1

Time Points for Cortisol Collection during the TSST



Area under the curve with respect to ground (AUC_g):

$$AUCg = \sum_{i=1}^{n-1} \frac{(m(i+1) + mi) * ti}{2}$$

where n is the total number of measurements,

m_i are the individual measurements,

and t is the time distance between measurements.

Area under the curve with respect to increase (AUC_i):

$$AUCi = \left(\sum_{i=1}^{n-1} \frac{(m(i+1) + mi) * ti}{2} \right) - \left(m1 * \sum_{i=1}^{n-1} ti \right)$$

where n is the total number of measurements,

m_i are the individual measurements,

and t is the time distance between measurements.

Twenty four hour integrated cortisol was calculated by dividing the total AUC_g for 24-hour by the time period of interest (24-h), which yielded µg/dl/hour. For the diurnal cortisol sample, $AUC_{g\text{-}diurnal/24h}$ was calculated; for the morning

cortisol sample, $AUC_{i\text{-}morning}$ and $AUC_{g\text{-}morning}$ were calculated; for the reactive cortisol sample (TSST), the $AUC_{i\text{-}TSST}$ and $AUC_{g\text{-}TSST}$ were calculated.

The AUC methodology is useful in limiting the number of statistical comparisons; since the number of repeated measures is irrelevant, it does not require α-level corrections. Moreover, this method is superior to the within subjects design ANOVA with repeated measure method since the ANOVA method cannot correct for non-identical time intervals between measurements. Moreover, the ANOVA method cannot differentiate between the information obtained in analyzing both the AUC_g and AUC_i, namely the total output of the system and the sensitivity of the system, respectively (Pruessner et al., 2003).

Procedure

The approval of the Research Ethic Board of the Douglas Hospital Research Centre was secured before each phase of the recruitment into this study: EnviroGen study; Stress, coping and schizophrenia study; and Trauma and cortisol study

Recruitment of chronic patients diagnosed with psychosis

There are 2 subgroups of chronic patients. One group was first recruited via the EnviroGen study (EG) (S. King, Laplante, & Joober, 2005), which investigates putative risk factors for schizophrenia. During the EG protocol, much information regarding genetic and environmental risk factors for schizophrenia was collected, as well as information regarding the course and outcome of the disorder. During the EnviroGen protocol, SCID, CTQ and BPRS data were collected.

Following their participation in the EG study, a number of patients from this study was later invited to participate in a study of stress, coping and cortisol in schizophrenia. During that study, patients underwent the TSST, and salivary cortisol was collected at 8 different time points. Subsequently, patients were approached for a study on childhood trauma and cortisol in schizophrenia, where basal cortisol data were collected (Braehler et al., 2005).

The second subgroup was also recruited initially after their participation in the EG project, where SCID, CTQ and BPRS data were collected. Following their participation in EG, they were approached for a study on the impact of childhood trauma on cortisol in schizophrenia, during which diurnal and morning cortisol

samples were collected. Lastly, these participants were recruited for a study on stress, coping and cortisol in schizophrenia, in which the TSST data were collected.

It is of note that the case managers of each patient, from both subgroups, were contacted before recruitment for each study, to confirm that the patients were stabilized and able to provide informed consent.

The EnviroGen project. Recruitment for the EnviroGen project was done via lists of patients done by the archives of the Douglas Hospital. Eligible patients were identified, and their case managers or psychiatrists were contacted to find out if each patient was stabilized, able to provide written consent, and if it was believed that the patient could undergo the study. Following this, a research assistant made an appointment with the patients' case manager for the time of their next visit, so that the case manager could introduce the research assistant to them. Once introduced, the research assistant presented the EnviroGen protocol, and verified if the patients were interested in participating. Patients who accepted participation were invited to the Douglas Hospital Research Centre, where they met with the research team and underwent an exhaustive research interview cataloguing most of the known environmental risk factors for schizophrenia; data on the course and outcome of the patients' illness were also collected. Subjects were also asked to give blood in order to collect genetic data. Depending on the patients, several interview sessions were needed. Moreover, subjects were asked to give consent for the research team to contact their mothers, so that independent interviews could be done with them to collect data on early environmental risk factors that the patients were unlikely to know (i.e. obstetric complications, prenatal stress).

Stress, coping and schizophrenia. Recruitment of subjects for the stress, coping and schizophrenia study was done via inviting subjects who previously underwent the EnviroGen protocol. Once these participants agreed to participate in the study, they were given an appointment in the afternoon at the Universté de Montréal to undergo the Trier Social Stress Test (TSST) – patients were reminded that they had to refrain from eating, smoking, drinking, brushing their teeth and exercising 1 hour before the experiment. Upon arrival, subjects were instructed in the method of saliva sampling, and were shown into a quiet room for 1 hour, where they

filled out questionnaires on stress and coping. Following this, participants were asked to give 2 saliva samples at 5 minutes intervals; these saliva samples were essentially buffers, and were later discarded. Five minutes after the collection of the second sample, a third saliva sample was collected, serving as baseline; five minutes later a fourth saliva sample was collected serving as a second baseline. Immediately following collection of the fourth sample, the experimenter explained to the subjects that they had to produce a 5 minutes speech on what they dislike about their physical appearance and that they had 10 minutes to prepare their speech. The subjects were also told that during the speech, 3 evaluators would be observing from behind a one-way mirror, analyzing and judging their discourse and their non-verbal behavior. Lastly, the participants were informed that immediately following the speech, they would be asked to perform mental arithmetic in front of the one-way mirror, subtracting 13 from 2083 serially, until 5 minutes elapsed; after each mistake, the patients were told to start again from 2083.

It is important to note that the judges behind the one-way mirror were, in fact, graduate students from the psychology department, who were only seen by the subjects when entering the interview room, and were in fact not present during the experiment.

Immediately following the anticipatory phase (after 10 minutes) a fifth saliva sample was collected, followed immediately by the task. Immediately following the speech and mental arithmetic tasks (after 10 minutes), a sixth saliva sample was collected. The seventh, eighth, ninth and tenth saliva samples were collected every 10 minutes after the collection of the sixth saliva sample, while the subjects were resting in a quiet room where a calm movie was presented (Over Canada, An aerial adventure). Following the collection of the last saliva sample, a brief evaluation of psychiatric symptoms was done using the BPRS.

Childhood trauma, cortisol and schizophrenia. Patients who completed the EnviroGen protocol and agreed to be contacted for further research were contacted for the childhood trauma, cortisol and schizophrenia project. During this research, patients were invited to the Douglas Hospital Research Centre, or were met in the community, and were instructed in the method of saliva sampling. Then, participants

were given careful explanations about the research protocol, which involved collecting 7 saliva samples at different times during the day: awakening; awakening +30 minutes; awakening +60 minutes; before lunch; 3 hours after lunch; at bedtime; and at awakening the following day. The importance of strict adherence to the research protocol was conveyed, and a sheet with the expected sampling times was done with the subjects, to help them remember exactly when the samples needed to be taken. Participants were told to put the samples taken in a freezer, and to return them all in a return envelope that was provided by the experimenter.

Involvement of the present candidate

Over the course of this project, the present candidate interviewed 16 EnviroGen subjects, directly recruiting 9 of them, and participated in the recruitment of an additional 3. Furthermore, the present candidate coordinated the EnviroGen project for a period of one year, as well as trained other interviewers who worked on the project. Moreover, the present candidate recruited and tested 12 subjects for the trauma study, and was directly involved in the recruitment of all patients of the stress, coping and schizophrenia study. Finally, the present candidate completed the literature review, as well as completed the statistical analysis.

Statistical Analysis

All primary analyses were done using multiple linear regressions, with a *a priori* α-level set a .05. The dependent variables for the analyses were: area under the curve with respect to increase (AUC_i) for the morning cortisol response, and following the TSST; the area under the curve with respect to ground (AUC_g) for the morning cortisol response and following the TSST; and 24-h integrated cortisol. The independent variables were the total score of the CTQ, and the Dysphoria subscale of the BPRS.

As previously noted in the literature, recent reports have shown that older subjects have greater cortisol reactivity. Moreover, some research has found that, after a public speaking and arithmetic task, men have greater cortisol reactivity compared to women. Taking these results into account, we decided to control for both Age and Sex.

After each analysis, the residual plots were investigated to make sure the assumptions of linear regression were met. First, by plotting the residuals vs. the predicted values, and verifying that the data points were distributed around a horizontal line, we made sure that our data met the assumption of linearity. Secondly, by looking at the same plots, and verifying that the residuals were evenly distributed, we made sure that our data met the assumption of homoscedasticity - namely, the homogeneity of the variance. Lastly, by looking at the normal probability plots of the residuals, we verified that our data met the assumption for normality, or that no extreme data points exerted a disproportionate influence on the parameters estimated.

It should also be noted that due to the exploratory nature of this study and the relatively small sample sizes, caution should be taken while interpreting the results.

Research Question 1: Morning and Diurnal cortisol

1A-Controlling for Age, Sex and Dysphoria, what is the association between self-reported childhood trauma and basal salivary cortisol?

i- secretion in the morning

$[AUC_{i\text{ - morning}}]$ = [control variables] + [CTQ total]

$[AUC_{g\text{ -morning}}]$ = [control variables] + [CTQ total]

ii-over a 24h period

$[AUC_{g\text{- diurnal/24h}}]$ = [control variables] + [CTQ total]

2B- Controlling for Age, Sex and Dysphoria, do self-reported childhood trauma and dysphoria interact to explain variance in basal cortisol?

i- secretion in the morning

$[AUC_{i\text{ - morning}}]$ = [control variables] + [CTQ total] + [CTQ total X Dysphoria]

$[AUC_{g\text{ - morning}}]$ = [control variables] + [CTQ total] + [CTQ total X Dysphoria]

ii- over a 24h period?

$[AUC_{g\text{ - diurnal/24-h}}]$ = [control variables] + [CTQ total] + [CTQ total X Dysphoria]

Research Question 2: Reactive cortisol

2A-Controlling for Age, Sex and Dysphoria, what is the association between self-reported childhood trauma and salivary cortisol reaction in response to a psychosocial stressor?

$[AUC_{i\text{-}TSST}]$ = [control variables] + [CTQ total]

$[AUC_{g\text{-}TSST}]$ = [control variables] + [CTQ total]

2B- Controlling for Age, Sex and Dysphoria, do self-reported childhood trauma and dysphoria interact to explain variance in cortisol reaction in response to a psychosocial stress?

$[AUC_{i\text{-}TSST}]$ = [control variables] + [CTQ total] + [CTQ total X Dysphoria]

$[AUC_{g\text{-}TSST}]$ = [control variables] + [CTQ total] + [CTQ total X Dysphoria]

RESULTS

All tables in this section can be found after the results section, pages 30 to 47

Characteristics of the participants

Descriptive variables

Of the 31 psychotic patients who accepted to participate in this research, 24 completed the diurnal cortisol portion of the study (which included the analyses for morning cortisol and 24-hour integrated cortisol). Of these 24 patients, 13 were diagnosed with paranoid schizophrenia, 6 with undifferentiated schizophrenia, 1 with disorganized schizophrenia, 1 with residual schizophrenia, 2 with schizoaffective disorder and 1 with schizophreniform disorder. There were 20 males and 4 females. Their mean age was 32.6 years old (*SD* =8.3).

Of the 31 psychotic patients who accepted to participate in this research 23 completed the reactive cortisol portion of the study (which included the TSST protocol). Of these 23 patients, 14 were diagnosed with paranoid schizophrenia, 4 with undifferentiated schizophrenia, 1 with disorganized schizophrenia, 1 with residual schizophrenia, 2 with schizoaffective disorder and 1 with schizophreniform disorder. There were 18 males and 5 females. Their mean age was 31.6 years old (*SD* =7.9). Seventeen patients participated in both parts of the study.

All but one female patient was taking neuroleptic medications at the time of the study; consequently, the data of that patient were excluded from analysis. This essentially removed one subject from both the analyses for basal and reactive cortisol.

Childhood trauma

Table 1 presents the different childhood trauma scores from the CTQ subscales and CTQ main scales for the 30 patients included in the analyses. The

scores for Total Trauma, the main independent variable, were explored to detect potential outliers. One subject had a score over 2 standard deviations above the mean; instead of removing the data for that subject, the score was "winsorised" to a maximum of 2 standard deviations above the mean (Tabachnick & Fidell, 1989). The score for that subject was still the highest score (for the original values of the winsorized scores, and their new values, please consult Appendix 1).

Symptom severity

Five patients were missing BPRS data. However, the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) had been completed with these patients, as part of another study. The BPRS has 4 items in the dysphoria factor, compared to 3 on the PANSS. The PANSS has similar items to the BPRS for depression, anxiety and guilt; however, the PANSS does not have a suicidality item like the BPRS. On the PANSS, suicidal ideations, if present, warrant a high depression score. Since none of the 5 subjects had a high depression score on the PANSS (they were all 0 or 1) it was possible to conclude that they would have had a score of 0 or 1 on the suicidality item of the BPRS. Taking this into account, and the PANSS scores on depression, anxiety and guilt, it was possible to estimate the score of the different items of the BPRS dysphoria subscale. The dysphoria score of these 5 subjects were thus estimated using the best estimate method proposed by Tabachnik and Fiddel (Tabachnick & Fidell, 1989), using all the accessible information known about the subject to estimate the missing values. Thus, for these 5 subjects, BPRS dysphoria was estimated by summing the PANSS rating for depression, guilt and anxiety, and by adding in the rating for depression a second time, as a proxy for suicidality. The mean BPRS dysphoria score of the whole sample was 7.5 (SD = 2.8) with a minimum of 4 and a maximum of 28, indicating relatively low scores. The data were explored for potential outliers, and all scores fell within 2 standard deviations around the mean

Cortisol measures

Salivary cortisol was measured (µg/dl) by specific radioimmunassays using a kit from DSL with small modifications. The limit of detection of the assays was 0.01 µg/dl. Individual time points for both the diurnal and TSST cortisol data were

explored for potential outliers. Outliers were carefully examined to detect if the variation was due to data entry errors or systematic bias in the data. It was detected that one patient with very high diurnal cortisol values was not taking her medication at the time of the study; her data were hence removed from further analysis. Moreover, there were 5 missing values for the TSST cortisol for the first baseline; we decided to remove the first baseline from the analysis, and use only the second baseline (Time 2). This essentially means that 8 scores went into the calculation of the different area under the curve values.

For the diurnal cortisol data, outliers were uncovered at awakening + 30, bedtime, and awakening the following day. For the TSST cortisol data, outliers were uncovered at Time 2, Time 3, Time 4, Time 6 and Time 8. All outliers were "winsorised" by giving the highest score a maximum of 2 standard deviations from the mean, and care was given to respect the relative distance between the different points. Table 2 presents the descriptive statistics after winsorization for the different area under the curve values calculated as dependent variables. Table 3 presents the correlations between the different CTQ subscales and the different area under the curve values calculated as dependent variables for the whole sample.

Full sample

For each dependent variable, we produced two basic models. The first model (Model 1) included all the covariates (Sex, Age and Dysphoria) as well as Childhood Trauma; the second model (Model 2) included all the covariates, Childhood Trauma, and introduced the interaction between Childhood Trauma and Dysphoria. In all models, a positive Beta coefficient for Age, Dysphoria and Childhood Trauma indicates a positive association with cortisol, while a negative beta indicates a negative association with cortisol. For the variable Sex, a positive Beta coefficient indicates that being a female is associated with higher cortisol levels, while a negative coefficient indicates that being a male is associated with higher cortisol levels.

Area Under the Curve Ground for Morning Cortisol

Table 4 shows the relevant statistics for the models. Model 1 explained 37% of the variance and was not quite significant ($F(4,19) = 2.74$, $p = .06$, adjusted $R^2 = .23$). However, in Model 1, there was a near-significant effect for Sex ($p=.08$),

showing a strong trend for women to have higher cortisol secretion in the morning. There also was a highly significant effect for Childhood Trauma (p=.01), indicating that lower cortisol secretion is associated with more severe Trauma scores. Model 2, including the interaction term between Trauma and Dysphoria, explained 37% of the variance and was not significant ($F(5,18) = 2.08$, $p > .05$, adjusted $R^2 = .19$). In Model 2, none of the variables had a significant effect. Moreover, the improvement in R-square going from Model 1 to Model 2 was not significant (p>.05).

In order to save degrees of freedom given our small sample size, and because Sex was the only near-significant covariate in model 1, we decided to test the Model with only Sex as a covariate. This yielded the significant Model 3, which explained 35% of the variance ($F(2, 21) = 5.63$, $p = .01$, adjusted $R^2 = .29$). In this model, the significant Beta for Sex ($p = .03$) indicates that female patients secreted more cortisol in the morning compared to men. The results from Model 3 also show that, controlling for Sex, more severe Childhood Trauma ($p = .01$) scores are associated with lower morning cortisol.

Because of the significant zero order correlation between the area under the curve ground for the morning cortisol and CTQ Total Childhood Abuse (but not for Neglect), we decided to explore the specific relationship between Abuse scores and morning cortisol secretion. These analyses were exploratory in nature, so care must be taken in interpreting the results. Table 5 shows the relevant statistics for the models. Model 1 explained 40% of the variance and was significant ($F(4,19) = 3.16$, $p = .04$, adjusted $R^2 = .27$). In that model, there was a near-significant effect for Sex ($p = .07$) and Childhood Abuse ($p = .01$). Model 2, including the interaction term between Abuse and Dysphoria, was not significant, explaining 41% of the variance ($F(5,18) = 2.45$, $p > .05$, adjusted $R^2 = .24$). In that model, there was, again, the near-significant effect only for Sex ($p = .07$), and Childhood Abuse. Moreover, the change in R-square, going from Model 1 to Model 2 was not significant ($p > .05$).

Furthermore, given the substantial correlation between the CTQ Emotional Abuse score and the area under the curve ground for morning cortisol, we also decided to explore the association between Emotional Abuse and morning cortisol. Again, these analyses were exploratory in nature, so care must be taken in

interpreting the results. Table 6 shows the relevant statistics for the models. Model 1 explained 40% of the variance and was significant ($F(4,19) = 3.18$, $p = .04$, adjusted $R^2 = .28$). In that model, there was a significant effect only for Emotional Abuse ($p = .01$). Model 2 was not quite significant, explaining 42% of the variance ($F(5,18) = 2.56$, $p = .06$, adjusted $R^2 = .25$). Moreover, the coefficient for the interaction, and the change in R-square, going from Model 1 to Model 2 were not significant ($p > .05$).

Area Under the Curve Increase for Morning Cortisol

Table 7 shows the relevant statistics for the models explaining variance in the AUC for morning cortisol secretion using the waking value (rather than zero) as ground, such that this dependent variable represents increase in cortisol above the waking value. Model 1 explained 10% of the variance and was not significant ($F(4,19) = .54$, $p > .05$, adjusted $R^2 = -.09$). In that model, none of the variables had a significant effect. Model 2, adding in the interaction term between Trauma and Dysphoria, explained 12% of the variance and was also not significant ($F(5,18) = .48$, $p > .05$, adjusted $R^2 = -.13$). Again, in that model, there was no significant effect for any of the variables, including the interaction term. Moreover, the change in R-square, going from Model 1 to Model 2 was not significant ($p > .05$).

Area Under the Curve for 24 hours Integrated Cortisol

Table 8 shows the relevant statistics for the models. Model 1 explained 30 % of the variance but was not significant ($F(4,19) = 2.1$, $p > .05$, adjusted $R^2 = .16$). However, even if the model was not significant, Childhood Trauma ($p = .03$) and Sex ($p = .02$) had significant coefficients, with higher levels of Trauma associated with lower 24-h integrated cortisol, and being a female associated with higher levels of 24-h integrated cortisol. Model 2 explained 31% of the variance and was also not significant ($F(5,18) = 1.62$, $p > .05$, adjusted $R^2 = .12$). In that model, only Sex had a significant effect ($p = .02$). Moreover, the change in R-square, going from Model 1 to Model 2 was not significant ($p > .05$).

In the planned models, the contribution of the covariate Age was negligible; given our small sample size, and in order to save degrees of freedom, we decided to trim out that covariate from the analysis. This yielded Model 3, which was close to being significant, and explained 30% of the variance ($F(3,20) = 2.90$, $p = .06$,

adjusted $R^2 = .20$). Moreover, in that model, the coefficients for Sex ($p = .01$) and Total Trauma ($p = .03$) were both significant.

Given the substantial zero order correlation between the CTQ Childhood Abuse and 24-hour integrated cortisol, we decided to explore the specific relationship between Abuse and 24-hour integrated cortisol, again, without Age as covariate. As mentioned earlier, these analyses were exploratory in nature, so care must be taken in interpreting the results. Table 9 shows the relevant statistics for the models. Model 1 explained 34% of the variance and was significant ($F(3,20) = 3.41$, $p = .04$, adjusted $R^2 = .24$). Moreover, for that model, there were significant effects for Sex ($p = .01$) and for Childhood Abuse ($p = .02$). Model 2, including the Abuse-by-Dysphoria interaction, explained 43% of the variance and was significant ($F(4,19) = 3.60$, $p = .02$, adjusted $R^2 = .31$). In that model, Sex was the only variable with a significant effect ($p = .03$). Furthermore, the change in R-square, going from Model 1 to Model 2 was not significant ($p > .05$).

Moreover, given the zero-order correlation between the CTQ Childhood Emotional Abuse and 24-hour integrated cortisol, we also decided to explore the Emotional Abuse and 24-hour integrated cortisol. Again, these analyses being exploratory, interpretation of their results must be done with care. Table 10 shows the relevant statistics for the resulting models, from which the covariate Age was trimmed out. The model (Model 1) explained 35% of the variance and was significant ($F(3,20) = 3.64$, $p = .03$, adjusted $R^2 = .26$). In that model, Sex ($p = .02$) and Emotional Abuse ($p = .01$) had significant effects. Model 2 was close to be significant ($F(4,19) = 2.84$, $p = .05$, adjusted $R^2 = .24$). In that model, none of the variables was significant. Moreover, the change in R-square, going from Model 1 to Model 2 was not significant ($p > .05$).

Area Under the Curve ground for TSST cortisol

The AUC_g value reflects the total cortisol secretion throughout the length of the TSST protocol. Table 11 shows the relevant statistics for the relevant models. Model 1 explained 19% of the variance but was not significant ($F(4,18) = 1.06$, $p > .05$, adjusted $R^2 = .01$). In that model, none of the variables had a significant effect. Model 2 explained 23% and was also not significant ($F(5, 17) = 1.00$, $p > .05$,

adjusted $R^2 = 0$). Again, none of the variables of that model had a significant effect. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Area Under the Curve increase for TSST cortisol

The AUCi value reflects the amount of cortisol secretion during the TSST protocol over-and-above the baseline cortisol sample. Table 12 shows the relevant statistics for the models. Model 1 explained 21% of the variance but was not significant ($F(4,18) = 1.17$, $p > .05$, adjusted $R^2 = .01$). In that model, none of the variables had a significant effect. Model 2 explained 23% and was also not significant ($F(5, 17) = .99$, $p > .05$, adjusted $R^2 = 0$). Again, none of the variables in that model had a significant effect. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Men only

Given that sex emerged as a significant independent variable in some of our models, and given the small number of females in our sample, limiting our ability to test the moderating effect of sex, we decided to repeat our analyses with the male participants only. Interesting results emerged for the cortisol during the TSST; however, the results for both the morning cortisol and for the 24-hour integrated cortisol essentially stayed the same. Thus, we will present here only the results pertaining to the TSST. The interested reader can find the relevant statistics for the analyses of the morning and 24-hour integrated cortisol in Appendix 2. Table 13 presents the correlations between the different CTQ subscales and the different area under the curves calculated as dependent variables for men only.

Area Under the Curve ground for TSST cortisol- Men only

Table 14 shows the relevant statistics for the produced models. Model 1 explained 25% of the variance but was not significant ($F(3,14) = 1.55$, $p > .05$, adjusted $R^2 = .09$). In that model, none of the variables had a significant effect, although there was a moderate trend for Trauma ($p = .10$), with higher level of trauma associated with higher cortisol increase. Model 2, introducing the interaction term Trauma by Dypshoria, was also not significant ($F(4,13) = 1.41$, $p > .05$, adjusted $R^2 = .09$) and explained 30% of the variance. Again, none of the variables had a

significant effect. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Given the significant zero order correlation between CTQ Childhood Abuse score and the area under the curve ground for cortisol during the TSST, and the near-zero correlation for Neglect, we decided to explore the relationship between Childhood Abuse and the area under the curve ground for the cortisol during the TSST. Table 15 shows the relevant statistics for the resulting models. Model 1, which included the variables Age, Dysphoria and Childhood Abuse, was significant, explaining 45% of the variance ($F(3,14) = 3.79$, $p = .03$, adjusted $R^2 = .33$). In that model, only Childhood Abuse was significant ($p = .01$). Model 2, which added the interaction term between Abuse and Dysphoria was not significant ($F(4,13) = 2.64$, $p > .05$, adjusted $R^2 = .28$) and explained 45% of the variance. In that model, none of the variables were significant. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Next, because of the significant correlation between the CTQ Childhood Sexual Abuse score and the area under the curve increase for cortisol during the TSST, we decided to also explore the relationship Sexual Abuse and the area under the curve increase for cortisol during the TSST. Table 16 summarizes the relevant statistics for the resulting model. Model 1, which included the variables Age, Dysphoria and Sexual Abuse, was significant, explaining 47% of the variance ($F(3,14) = 4.62$, $p = .02$, adjusted $R^2 = .39$). In that model, only Sexual Abuse was significant ($p < .01$). Model 2 included the interaction term Sexual Abuse by Dysphoria, and was also significant ($F(4,13) = 3.47$, $p = .04$, adjusted $R^2 = .37$), explaining 52% of the variance. In that model, none of the variables nor the interaction term were significant. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Area Under the Curve increase for TSST cortisol- Men only

As noted earlier, the AUC_i value reflects the cortisol secretion during the TSST over-and-above the baseline level. Table 17 shows the relevant statistics for the models. Model 1 explained 62% of the variance and was significant ($F(3,14) = 7.73$, $p = .003$, adjusted $R^2 = .54$). In that model, Dysphoria and Childhood Trauma had

significant effects ($p < .01$). The negative coefficient for Dysphoria indicates that higher levels of depression are related to a more blunted cortisol response, while the positive coefficient of Trauma indicates that higher level of trauma are related to a higher cortisol response. Model 2 was also significant ($F(4,13) = 5.49$, $p = .01$, adjusted $R^2 = .51$) and explained 63% of the variance. However, in the model, none of the variables were significant. Moreover, the 1% change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Given the significant zero order correlation between CTQ Childhood Abuse and the area under the curve increase for cortisol during the TSST, and not for Neglect, we decided to explore the relationship between Abuse and area under the curve increase for cortisol during the TSST. Table 18 shows the relevant statistics for the resulting models. Model 1 was significant, explaining 46% of the variance ($F(3,14) = 3.95$, $p = .03$, adjusted $R^2 = .34$). In that model, there was significant effect for Dysphoria ($p = .03$), and a near-significant effect for Childhood Abuse ($p = .08$). Model 2 explained 46% of the variance, but was not significant ($F(4,13) = 2.76$, $p > .05$, adjusted $R^2 = .29$). In that model, none of the variables were significant. Moreover, the change in R-square, going from Model 1 to Model 2, was not significant ($p > .05$).

Table 1

Descriptive Statistics – Childhood Trauma

CTQ scores (n=30)	Mean	Std. Deviation
Emotional Abuse	9.93	4.95
Physical Abuse	8.53	5.10
Sexual Abuse	7.70	2.91
Emotional Neglect	10.40	3.86
Physical Neglect	7.67	2.83
CTQ Abuse Total	26.14	10.87
CTQ Neglect Total	18.06	5.76
CTQ Total	43.60	12.61

Table 2

Descriptive Statistics – Area Under the Curve Values

	n	Minimum	Maximum	Mean	Std. Deviation
TSST AUC ground	22	5.28	43.96	16.67	10.15
TSST AUC increase	22	-32.89	17.70	1.44	10.96
Morning AUC ground	23	4.20	35.33	15.91	7.43
Morning AUC increase	23	-7.11	10.59	.95	4.44
24h integrated cortisol	23	.08	.29	.15	.05

Table 3

Correlations – Covariates, Childhood Trauma and Area Cortisol Values

	TSST AUC_{ground} n=23	TSST $AUC_{increase}$ n=23	Morning AUC_{ground} N=24	Morning $AUC_{increase}$ n=24	24-h integrated n=24
Sex	-.19	.10	.21	-.06	.28
Age	.34	.16	-.01	-.28	.02
Dysphoria	-.02	-.30	.30	.02	-.04
Emotional Abuse	.20	.19	-.44*	-.16	-.38
Physical Abuse	.19	.15	-.43*	-.18	-.25
Sexual Abuse	.33	.25	-.25	.19	.03
Emotional Neglect	-.09	.21	-.10	-.03	.07
Physical Neglect	-.13	.07	-.31	.27	-.17
Total Abuse	.29	.25	-.46*	-.11	-.29
Total Neglect	-.13	.17	-.22	.11	-.04
Trauma Total	.18	.28	-.42*	-.11	-.23

Note. * Correlation is significant at the 0.05 level (2-tailed).

Table 4

Childhood Trauma and Morning AUC ground

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	16.52	9.95		1.66	.11
	Age	.11	.18	.12	.61	.55
	Sex	8.35	4.50	.43	1.85	.08
	Dysphoria	.29	.57	.11	.50	.62
	Childhood Trauma	-.35	.13	-.58	-2.77	.01
2	Constant	16.74	17.40		.96	.35
	Age	.11	.18	.12	.59	.56
	Sex	8.33	4.82	.43	1.73	.10
	Dysphoria	.26	1.94	.10	.13	.90
	Childhood Trauma	-.36	.30	-.58	-1.20	.25
	Trauma X Dysphoria	.00	.04	.01	.02	.99
3	Constant	22.27	5.52		4.03	$p<.01$
	Sex	8.77	3.74	.45	2.35	.03
	Childhood Trauma	-.37	.12	-.60	-3.13	.01

Note. n=23

Table 5

Childhood Abuse and Morning AUC ground

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	10.83	8.92		1.21	.24
	Age	.33	.55	.13	.60	.56
	Sex	8.13	4.30	.42	1.89	.07
	Dysphoria	.12	.17	.14	.72	.48
	Childhood Abuse	-.39	.13	-.60	-3.03	.01
2	Constant	6.71	13.39		.50	.62
	Age	.85	1.35	.32	.63	.54
	Sex	8.93	4.78	.46	1.87	.08
	Dysphoria	.13	.18	.15	.74	.47
	Childhood Abuse	-.28	.29	-.44	-.99	.34
	Abuse X Dysphoria	-.02	.05	-.28	-.42	.68

Note. n=23

Table 6

Childhood Emotional Abuse and Morning AUC ground

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	5.69	8.63		.66	.52
	Age	.73	.53	.28	1.37	.19
	Sex	6.27	4.06	.32	1.55	.14
	Dysphoria	.21	.17	.23	1.18	.25
	Emotional Abuse	-.84	.28	-.57	-3.04	.01
2	Constant	12.33	13.38		.92	.37
	Age	.08	1.12	.03	.07	.94
	Sex	4.91	4.61	.25	1.07	.30
	Dysphoria	.18	.18	.20	1.01	.33
	Emotional Abuse	-1.21	.63	-.83	-1.92	.07
	Emotional Abuse X Dysphoria	.06	.08	.42	.66	.52

Note. n=23

Table 7

Childhood Trauma and Morning AUC increase

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	9.93	7.08		1.40	.18
	Age	-.17	.12	-.32	-1.38	.18
	Sex	-1.00	3.20	-.09	-.31	.76
	Dysphoria	-.09	.41	-.06	-.22	.83
	Childhood Trauma	-.03	.09	-.09	-.38	.71
2	Constant	4.46	12.27		.36	.72
	Age	-.17	.13	-.31	-1.30	.21
	Sex	-.47	3.40	-.04	-.14	.89
	Dysphoria	.63	1.36	.40	.46	.65
	Childhood Trauma	.07	.21	.19	.33	.74
	Trauma X Dysphoria	-.02	.03	-.55	-.55	.59

Note. n=23

Table 8

Childhood Trauma and 24-Hour Integrated Cortisol

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	.18	.08		2.36	.03
	Age	.00	.00	.06	.29	.77
	Sex	.09	.04	.63	2.62	.02
	Dysphoria	-.01	.00	-.33	-1.44	.17
	Childhood Trauma	.00	.00	-.50	-2.30	.03
2	Constant	.15	.13		1.11	.28
	Age	.00	.00	.07	.31	.76
	Sex	.09	.04	.66	2.54	.02
	Dysphoria	.00	.02	-.11	-.14	.89
	Childhood Trauma	.00	.00	-.37	-.72	.48
	Trauma X Dysphoria	.00	.00	-.27	-.30	.77
3	Constant	.20	.05		3.99	$p>.01$
	Sex	.09	.03	.62	2.67	.01
	Dysphoria	-.01	.00	-.34	-1.58	.13
	Childhood Trauma	.00	.00	-.50	-2.36	.03

Note. n=23

Table 9

Childhood Abuse and 24-Hour Integrated Cortisol

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	.17	.04		4.18	$p<.01$
	Sex	.09	.03	.62	2.77	.01
	Dysphoria	-.01	.00	-.33	-1.60	.12
	Childhood Abuse	.00	.00	-.53	-2.63	.02
2	Constant	-.06	.13		-.44	.66
	Sex	.31	.13	2.17	2.39	.03
	Dysphoria	-.01	.00	-.38	-1.93	.07
	Childhood Abuse	.00	.00	.81	1.03	.32
	Abuse X Dysphoria	-.01	.00	-2.41	-1.76	.09

Note. n=23

Table 10

Childhood Emotional Abuse and 24 hours Integrated Cortisol

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	.16	.04		4.15	$p<.01$
	Sex	.07	.03	.52	2.52	.02
	Dysphoria	.00	.00	-.22	-1.11	.28
	Emotional Abuse	-.01	.00	-.51	-2.74	.01
2	Constant	.07	.12		.60	.56
	Sex	.14	.09	.99	1.59	.13
	Dysphoria	.00	.00	-.13	-.59	.56
	Emotional Abuse	.00	.01	.06	.08	.94
	Emotional X Dysphoria	-.01	.01	-.88	-.80	.43

Note. n=23

Table 11

Childhood Trauma and TSST AUC ground

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	-1.36	14.46		-.09	.93
	Age	.41	.28	.32	1.47	.16
	Sex	-6.10	5.79	-.25	-1.05	.31
	Dysphoria	.52	.88	.14	.59	.57
	Childhood Trauma	.19	.19	.22	.98	.34
2	Constant	-2.87	25.93		-.81	.43
	Age	.39	.28	.30	1.39	.18
	Sex	-6.31	5.83	-.26	-1.08	.29
	Dysphoria	3.17	3.05	.84	1.04	.31
	Childhood Trauma	.64	.53	.73	1.20	.25
	Trauma X Dysphoria	-.06	.06	-.87	-.91	.38

Note. n=22

Table 12

Childhood Trauma and TSST AUC increase

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	-7.91	15.46		-.51	.61
	Age	.16	.30	.12	.55	.59
	Sex	5.65	6.19	.22	.91	.37
	Dysphoria	-1.46	.95	-.36	-1.54	.14
	Childhood Trauma	.20	.21	.21	.96	.35
2	Constant	7.04	28.05		.25	.80
	Age	.18	.30	.13	.59	.56
	Sex	5.81	6.30	.22	.92	.37
	Dysphoria	-3.48	3.30	-.86	-1.06	.31
	Childhood Trauma	-.15	.57	-.15	-.25	.80
	Trauma X Dysphoria	.04	.07	.62	.64	.53

Note. n=22

Table 13

Correlations – Covariates, Childhood Trauma and Area under the Curve values – **Men Only**

	TSST AUC_{ground} n=25	TSST $AUC_{increase}$ n=25	Morning AUC_{ground} n=25	Morning $AUC_{increase}$ n=25	24h integrated n=25
Age of participant	.29	.07	-.02	-.32	.12
Dysphoria	.03	-.57*	.16	.11	-.14
Emotional Abuse	.43	.32	-.73*	.01	-.44
Physical Abuse	.45	.34	-.46*	.04	-.30
Sexual Abuse	.62*	.47	-.54*	.17	-.33
Emotional Neglect	.01	.39	-.10	-.04	.03
Physical Neglect	-.10	.17	-.40	.34	-.26
Total Abuse	.63*	.47*	-.64*	.05	-.40
Total Neglect	-.05	.34	-.27	.14	-.10
Trauma Total	.47*	.56*	-.62*	.05	-.37

Note. * Correlation is significant at the 0.05 level (2-tailed).

Table 14

Childhood Trauma and TSST AUC ground – Men Only

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	-11.26	15.86		-.71	.49
	Age	.22	.31	.17	.70	.49
	Dysphoria	.34	1.09	.07	.31	.76
	Childhood Trauma	.44	.25	.42	1.75	.10
2	Constant	-4.00	33.16		-1.21	.25
	Age	.25	.31	.19	.78	.45
	Dysphoria	4.21	4.07	.90	1.03	.32
	Childhood Trauma	1.15	.76	1.10	1.51	.15
	Trauma X Dysphoria	-.10	.10	-1.07	-.99	.34

Note. n=17

Table 15

Childhood Abuse and TSST AUC ground – Men Only

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	-16.95	13.35		-1.27	.23
	Age	.24	.26	.18	.90	.38
	Dysphoria	.82	.95	.18	.86	.40
	Childhood Abuse	.83	.27	.62	3.04	.01
2	Constant	-16.08	25.22		-.64	.53
	Age	.23	.28	.18	.85	.41
	Dysphoria	.70	3.12	.15	.22	.83
	Childhood Abuse	.79	.91	.60	.87	.40
	Abuse X Dysphoria	.01	.13	.03	.04	.97

Note. n=17

Table 16

Childhood Sexual Abuse and TSST AUC ground – Men Only

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	-2.76	13.12		-1.58	.14
	Age	.40	.25	.31	1.63	.13
	Dysphoria	.85	.91	.18	.93	.37
	Sexual Abuse	2.47	.73	.65	3.39	$p<.01$
2	Constant	-11.88	18.31		-.65	.53
	Age	.44	.26	.34	1.71	.11
	Dysphoria	-.78	2.48	-.17	-.32	.76
	Sexual Abuse	1.11	2.05	.29	.54	.60
	Sexual Abuse X Dysphoria	.22	.31	.48	.71	.49

Note. n=17

Table 17

Childhood Trauma and TSST AUC increase – Men Only

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	.30	12.11		.02	.98
	Age	-.22	.24	-.16	-.91	.38
	Dysphoria	-2.80	.83	-.55	-3.36	$p<.01$
	Childhood Trauma	.65	.19	.57	3.34	$p<.01$
2	Constant	9.76	26.08		.37	.71
	Age	-.23	.25	-.16	-.91	.38
	Dysphoria	-4.07	3.20	-.81	-1.27	.23
	Childhood Trauma	.41	.60	.37	.69	.50
	Trauma X Dysphoria	.03	.08	.33	.41	.69

Note. n=17

Table 18

Childhood Abuse and TSST AUC increase – Men Only

Model		Unstandardized Coefficients		Standardized Coefficients	t	p-value
		B	Std. Error	Beta		
1	Constant	8.23	14.26		.58	.57
	Age	-.08	.28	-.06	-.29	.78
	Dysphoria	-2.51	1.02	-.50	-2.48	.03
	Childhood Abuse	.54	.29	.38	1.87	.08
2	Constant	10.98	26.92		.41	.69
	Age	-.09	.29	-.06	-.30	.77
	Dysphoria	-2.90	3.33	-.58	-.87	.40
	Childhood Abuse	.43	.97	.30	.45	.66
	Abuse X Dysphoria	.02	.14	.10	.12	.90

Note. n=17

DISCUSSION

Overview of research

The main objectives of this study were first to clarify the role of childhood trauma in the basal and reactive cortisol profiles of psychotic patients; secondly, we aimed to determine to what extent depression interacts with childhood trauma in explaining the basal and reactive cortisol profiles of these patients.

As hypothesized, our results showed that, controlling for age, sex, and dysphoria, more severe childhood maltreatment is associated with lower rates of total basal cortisol output in the morning and over 24 hours; the various models explained up to 37% of the variance. Moreover, our exploratory results indicate that it may be important to look at specific types of maltreatment rather than to look at trauma in general, and that emotional abuse during childhood may be a particularly important variable in explaining total cortisol output during the morning; using the abuse score rather than the total score tended to explain an additional 3% - 5% of the variance in basal cortisol. However, contrary to our hypothesis, our results did not show an association between childhood maltreatment and the sensitivity of the HPA axis during the morning, the basic model explaining only 10% of the variance in AUC-increase. In addition, our results did not support the hypothesized moderating role of depression on childhood trauma when explaining the basal cortisol profiles of patients with psychosis.

As for reactive cortisol, contrary to our hypothesis, when looking at our full sample, childhood trauma was not associated with levels of cortisol in reaction to a psychosocial stressor, even when looking at subtypes of trauma. The models tested explained less then 25% of the variance in TSST cortisol. However, when we repeated the analyses with only men, reducing our sample to 17 subjects, our results showed that psychotic men with greater childhood trauma scores had a more sensitive HPA axis, with the specific models explaining up to 62% of the variance: in all model, more severe trauma was associated with greater increases in salivary cortisol in reaction to the psychosocial stress. Moreover, our exploratory results again showed the importance of looking at specific types of trauma: sexual abuse in psychotic men was indeed associated with a higher cortisol output during a

psychosocial stress; its specific model explaining 47% of the variance. While other types of abuse may also play a role, using only sexual abuse as a predictor explains as much variance as using total abuse alone (which explains 45%). Once more, our results did not support the moderating role of depression on childhood trauma when explaining the reactive cortisol profiles of patients with psychosis.

In conclusion, in a group of psychotic patients, the more severe the reported childhood trauma, the lower the levels of total cortisol output secreted during both the morning and over 24 hours. In some case, additional variance is explained when only childhood abuse, and not neglect, is considered. Moreover, in psychotic men, more severe childhood trauma seems to be associated with a greater increase in cortisol in the face of a psychosocial stressor.

Role of covariates

Sex

In general, being a female with psychosis is associated with higher basal levels of cortisol in both morning and over 24h. While our results go against those found by other groups studying healthy subjects in which there is no gender difference (Edwards, Clow, Evans, & Hucklebridge, 2001; Takai et al., 2007), they are in the same line as another study (Pruessner et al., 1997) that found higher cortisol levels in women. However, we did not control for the possible impact of oral contraceptive on cortisol levels, which may explain our findings. However, this is unlikely since oral contraceptives seem to be associated with a smaller basal cortisol secretion (Korszun et al., 2002; Pruessner et al., 1997).

Our results show no association between sex and our measures of reactive cortisol. This is surprising considering that other groups found that adult women have a more blunted cortisol response then men after a psychosocial stress (Kajantie & Phillips, 2006). Yet, our results are similar to a recent meta-analysis which found no gender differences in reactive cortisol for adults of approximately the same age group (23.5 years old) as our sample (Kudielka et al., 2004). However, not controlling for menstrual cycle, which was previously shown to be significantly associated with the cortisol response following a psychosocial stress in healthy

subjects (C. Kirschbaum, Kudielka, B.M., Gaab, J., Schommer, N.C., Hellhammer, D.H., 1999), may have masked a significant impact of gender on these results.

Because of the small number of females who completed the study (4 for the basal cortisol and 5 for the reactive cortisol analyses), our results regarding the sex variable must be interpreted with caution. In addition, the small number of females led us to conduct additional analyses, using a group composed of only men. While removing the women from the analyses yielded a sample size of only 17 subjects, it resulted in a radical increase in the magnitudes of the different zero-order correlations, particularly between the different childhood maltreatment scores and the area under the curve scores for TSST, and the area under the curve ground for the morning cortisol. In general, these secondary analyses show that, in psychotic men, the sensitivity of the HPA axis during a psychosocial stress is associated with the presence of childhood trauma, a conclusion we could not make based on the results from the combined sample. Thus, although we had too few females to test interactions between sex and childhood trauma, our results, when eliminating the women from the sample, suggest that sex is indeed an important moderating variable. We will discuss these results in greater details later.

Age

Our results do not support an association between age and cortisol for any of our cortisol variables. This conclusion is similar to that of other studies using relatively young subjects, where no age effects are found for adults and adolescents for both morning cortisol (Wust et al., 2000) and for cortisol following the TSST (Kudielka et al., 2004). Moreover, it is important to note that our sample is also relatively young; in the literature, a significant effect for age seems to appear only when older participants (over 60 years old) are included in the sample (Kudielka et al., 2004).

Dypsphoria

When looking at our full sample, dysphoria is not significantly related to any cortisol measures. This is surprising considering the robust findings in the literature linking depression with both hypercorticolism and a blunted cortisol response following a psychosocial stress (Burke et al., 2005). However, as expected, when

looking at psychotic men only, higher levels of dysphoria are associated with a more blunted cortisol response following psychosocial stress (Burke et al., 2005). Yet, care must be taken in interpreting our results since the majority of our participants had low depression scores, reducing the variance available to detect a significant correlation. Finally, although dysphoria was assessed on the same day as reactive cortisol, basal cortisol was assessed on a different day, which may also have reduced the correlation.

Role of Childhood trauma

In basal cortisol

Our results show that, in psychotic patients, childhood maltreatment is significantly associated with the total cortisol output secreted during the morning, and to a lesser extent, to the total cortisol output secreted during 24 hours: higher trauma is consistently linked to lower cortisol levels. These results are in line with those found in adult women who were victims of childhood maltreatment (C. Heim et al., 2001; Weissbecker et al., 2005) as well as in patients diagnosed with post-traumatic stress disorder (Luecken, Dausch, Gulla, Hong, & Compas, 2004). Our results suggest that, in psychotic patients, when assessed in term of total cortisol output, an abnormality of the unmanipulated HPA axis is associated with early trauma. However, our results do not support that, in psychotic patients, when assessed in term of the sensitivity of the awakening cortisol response, there is an abnormality of the unmanipulated HPA axis associated with early trauma.

In reactive cortisol

Our initial results, with the full sample, show no relation between reactive cortisol and childhood trauma. However, after repeating the analyses with men only, an interesting pattern develops. While care must be taken in interpreting these secondary analysis drawn from a smaller sample size, it appear that, in psychotic men, the sensitivity of the HPA axis during psychosocial stress is greatly influenced by the presence of childhood trauma, with higher trauma levels associated with a higher cortisol response – indeed, the total variance explained by looking at men only (62%) is much larger then by looking at the combined sample (21%). Moreover, in psychotic men, the total cortisol output secreted during psychosocial stress is highly associated with childhood abuse; while childhood trauma explains only 25% of the

variance, childhood abuse explains 45%. Similarly to childhood trauma, higher levels of abuse are associated with a greater total cortisol output. Furthermore, the substantial zero-order correlation between childhood neglect and the sensitivity of the HPA axis during psychosocial stress in men suggests that neglect could have a non-negligible effect in this group. However, our sample size does not permit us to draw definite conclusions about the role of neglect on the reactive cortisol profiles of psychotic men.

It is of note that these results are in line with previous research showing that men have a greater cortisol reactivity then women after a public speaking task. By removing the women, who have a more blunted response, we raised the signal to noise ratio, essentially maximizing the variance and making statistical significance easier to obtain. Yet, it should also be noted that albeit the results of the full sample were far from statistical significance, they were in the direction expected, suggesting that a larger sample size may have detected a significant effect.

The results with the sample composed of men only are reminiscent of those found in patients diagnosed with PTSD, who also show a greater HPA response following a psychosocial stress (McRae et al., 2006). Moreover, it is interesting to note that our results run contrary to those found in healthy adults victim of childhood trauma and without a diagnosis of PTSD (Carpenter et al., 2007). Indeed, in these healthy adults, it was found that higher levels of maltreatment are significantly associated with lower levels of cortisol following a psychosocial stress. Contrary to these results, we found higher cortisol reactivity in our male psychiatric sample These results suggest that psychotic patients victim of childhood maltreatment show an abnormality in their stress response, possibly similar to that found in PTSD patients, that is essentially different from that found in healthy subjects also victim of childhood trauma. Indeed, it appears that while patient with PTSD and psychotic patients victim of early maltreatment have a higher cortisol response from psychosocial stress, healthy subjects with childhood trauma and no PTSD have a lower cortisol response; the higher cortisol response is hence possibly a function of some trauma and the presence of a disorder, instead of the presence of a trauma alone.

Importance of type of maltreatment

Abuse vs. Neglect

While we found strong associations between childhood abuse and both basal and reactive cortisol in adults suffering from psychosis, with exploratory models explaining up to 40% of the variance in the full sample, we did not find any relationship between childhood neglect and any of our cortisol variables. This goes against previous studies showing that neglected children have altered basal cortisol levels compared to controls (De Bellis et al., 1999; Gunnar et al., 2001), and that childhood emotional neglect is strongly associated with a blunted cortisol response to a psychosocial stress in healthy adults (Carpenter et al., 2007). It is possible that our sample size was not sufficiently large enough to detect a significant impact of childhood neglect on cortisol; this seems particularly possible given the substantial correlation between childhood neglect and the sensitivity of the HPA axis during psychosocial stress in psychotic men. Conversely, it could also be possible that something specific about childhood abuse causes these results. However, no research to date has specifically looked at the different impact of childhood abuse and childhood neglect on the development of the HPA axis. Alternatively, it is also possible that abuse and neglect have a different impact on those already at risk for psychotic disorders (via other risk factors such as genetic predisposition), leading to different alterations of the HPA axis compared to healthy adults victim of childhood trauma.

Different types of abuse

In addition to showing the importance of childhood abuse, rather than neglect, in the cortisol profiles of psychotic patients, our exploratory results suggest that looking at specific types of abuse may give a clearer picture of the putative causes of HPA abnormalities in psychotic patients.

Emotional abuse

Emotional abuse was previously shown to be an important risk factor in explaining more severe dissociative symptoms in chronic schizophrenia (Holowka, King, Saheb, Pukall, & Brunet, 2003), as well as in a first episode sample and in normal controls (Valiquette et al., in preparation). Moreover, dissociation has been shown to be correlated with diurnal cortisol (higher dissociation being linked to lower

basal cortisol levels) (Simeon, Knutelska, Yehuda et al., 2006) as well as cortisol levels following stress (higher dissociation being linked to a greater cortisol response) (Simeon, Knutelska, Smith, Baker, & Hollander, 2006). Furthermore, it was previously shown that emotional abuse is negatively associated with cortisol in the first hours after waking (Braehler et al., 2005). Our results support these previous findings by replicating the strong association between more severe childhood emotional abuse and lower total cortisol secreted during both the morning and during 24 hours, with specific models explaining up to 47% of the variance. Moreover, our results complete the link between emotional abuse and dissociation, and between dissociation and greater reactive cortisol, by seeing a direct effect of higher emotional abuse on greater reactive cortisol.

These results strongly suggest that emotional abuse may have an important etiological role in the abnormal stress response found in psychotic patients. These results are also particularly important, since items on emotional abuse are not typically included in many psychometric scales measuring maltreatment during childhood. Obviously, emotional abuse appears to be very salient and should receive greater attention.

Sexual abuse

Childhood sexual abuse has been shown to be a risk factor for a variety of adult psychiatric disorders (Spataro, Mullen, Burgess, Wells, & Moss, 2004). Similarly to emotional abuse, sexual abuse has also been linked to dissociative symptoms in patients diagnosed with psychosis (Holowka et al., 2003), as well as in controls (Valiquette et al., in preparation). Moreover, sexual abuse has been shown to be negatively related to cortisol during the first hours after waking (Braehler et al., 2005) and it has also been positively associated with cortisol levels following a psychosocial stress (Carpenter et al., 2007).

Our results support these previous findings, and suggest that, in men, sexual abuse may be as good of a predictor of the total cortisol output during a psychosocial stress than is total childhood abuse (combining emotional, physical and sexual abuse), childhood abuse explaining 45% of the variance and sexual abuse explaining 47%. This suggests that, while other forms of abuse may be important, childhood sexual

abuse is particularly relevant. The substantive correlations between sexual abuse and the different cortisol measures in the full sample also suggest that this may generalizes to both males and females – however, our sample size does not permit us to draw definite conclusions.

Taken together, these results suggest a particularly salient etiological role for childhood sexual abuse in the abnormal stress response of male psychotic patients.

Physical abuse

Childhood physical abuse has also been shown to be a risk factor for adult psychopathology (Saleptsi et al., 2004). It has been linked with dissociative symptoms in adult psychotic patients (Holowka et al., 2003), and in controls (Valiquette, in preparation). It has also been linked, to some extent, to the abnormal stress response of otherwise healthy adults (Carpenter et al., 2007). Our results suggest that, while physical abuse may not be a predictor of the sensitivity of the HPA axis, either during the morning or after a psychosocial stress, it may be a predictor of the total cortisol output during the morning.

While future studies should further investigate the role of specific types of childhood abuse on the development of the HPA axis, taken together, our results suggest that looking at different types of childhood abuse may help better characterize the abnormal stress response found in patients with psychosis.

Moderating role of dysphoria

Based on research showing different cortisol profiles in psychiatric patients suffering from major depression or PTSD, with and without childhood trauma (Breier, 1989; Bremner, Vythilingam, Anderson et al., 2003; Elzinga et al., 2003; C. Heim et al., 2000), we hypothesized that depression could play a moderating role on childhood trauma when explaining the cortisol profiles of psychotic patients. Specifically, we hypothesized that patients reporting both high trauma and high dysphoria would present the lowest basal cortisol as well as the highest cortisol response after a psychosocial stress.

However, we did not find any interaction between trauma and depression for any of our cortisol variables. While it is possible that there is something specific about the abnormality of the HPA axis in psychotic patients that renders the level of

dysphoria irrelevant, it is important to note that most of our participants had low depression scores; it is hence possible that the interaction would have appeared had we included more participants with higher depression levels. Our small sample size, coupled with the low depression scores of the participants, do not permit us to draw definite conclusions on the possible moderating role of depression – further studies, with patients with low and high trauma levels, as well as low and high depression levels, would be required to elucidate this.

Limitations

As previously noted, important limitations have a negative impact on the generalizability of our results. Mainly, our relatively small sample size considerably limits our power to detect small, but meaningful effects. Moreover, regressing a large number of variables with a small sample may have led to model instability. However, we did attempt to respond to this problem by having parsimonious final models, which were obtained by trimming out the non significant variables. This led the final models to have between 3 and 4 predictors, yielding a number of subjects/number of predictor ratio (n/k) between 5.66 and 5.75. We acknowledge that this is still at the lower end of the suggested n/k ratios for multiple regressions

Furthermore, during this study, many statistical tests were produced, each yielding a small chance of detecting a significant effect; consequently, increasing the number of tests by doing exploratory and secondary analysis increased our chances of detecting significant results when there were none. Conscious of the seriousness of this limitation, we applied a Bonferroni correction to the *a priori* α-level of .05, considering each dependent variable as a separate experiment. This yielded a corrected α -level of .02 for all comparisons. After the correction, only two models remained significant: the model with the area under the curve increase during the morning regressed on total childhood trauma, and the area under the curve increase after the TSST for men only regressed on total childhood trauma. This leads us to be more confident in these specific results

Two other limitations regarding our sample warrant attention. First, the small number of females in our sample does not permit us to adequately test the possible interaction between gender and early trauma in psychotic patients. Moreover, the

lack of control group prevents us from concluding that our results are specific to patients with a psychotic disorder.

Additional limitations, not linked to the sample, must be noted. First, as explained in the procedure section, the data were not all collected at the same time. Since some variables are known to vary over time, like depression, this may have had a critical impact on the results. Moreover, home salivary cortisol collection for the basal measures may not have been reliable. In fact, it has been shown that compliance to scientific protocol by research participants can be as low as 62% in normal controls (Broderick, Arnold, Kudielka, & Kirschbaum, 2004); since patients suffering from psychotic disorders are known to have cognitive deficits, as well as withdrawal symptoms, it is possible that strict compliance to our research protocol may have been even lower. Furthermore, morning cortisol has been shown to be influenced by situational factors, and that up to 6 collection days may be necessary to obtain reliable measures (Hellhammer et al., 2007); our study included only a single day of collection.

Finally, we did not control for an important potential confound: trauma after childhood. The huge literature on PTSD clearly demonstrates that adult trauma can have a serious impact on the HPA axis. It is conceivable that patients who were victim of childhood trauma are also more likely to be victim of adult trauma, and that adult trauma is in fact driving our results. Moreover, the scale (CTQ) used to assess trauma does not make a distinction between acute and chronic trauma. The impact of one very traumatic event during brain development may have very different consequences than the impact of relatively mild but chronic traumatic experiences. Future studies should take these limitations in consideration.

CONCLUSION

This is the first study investigating the relationship between childhood trauma and the cortisol response following a psychosocial stress in patients diagnosed with a psychotic disorder. Moreover, contrary to other studies investigating the cortisol profiles of psychotic patients, the current study has a relatively homogeneous group in term of age (all patients were relatively young) and diagnosis (most patients were diagnosed with one subtype of schizophrenia). Especially important is the fact that

all patients were chronic users of antipsychotic medications, which was previously shown not to have an impact on the cortisol profiles of patients (Kaneda et al., 2002; Meador-Woodruff & Greden, 1988).

Our results, coupled with results from studies of childhood trauma in people with anxiety and affective disorders (C. Heim & Nemeroff, 1999), as well as studies of childhood trauma in healthy adults (Carpenter et al., 2007), support the idea that HPA dysregulation is a marker of childhood maltreatment, irrespective of diagnosis. It appears that, even if the mechanisms of action of childhood trauma may differ depending on the presence or absence of a psychiatric diagnosis, or with particular psychiatric diagnoses, childhood trauma is a non-specific risk factor for a host of adult psychopathologies, including psychotic disorders. The exact emerging diagnosis is likely to be determined by other etiological risk factors, such as genetic predisposition. Alternatively, it is also possible that a dysregulated HPA axis prior to childhood trauma may lead to a more exaggerated response to the stressor, which could itself be a risk factor for later psychopathology.

The impact of childhood maltreatment on the HPA axis in male psychotic patients is similar to that which is found in patients with PTSD: low basal cortisol levels (Yehuda, 1998) and hypereactivity of the HPA axis in response to a psychosocial stress (C. Heim, Newport, DJ, Heit, S, Graham, YP, Wilcox, M, Bonsall, R, Miller, AH, Nemeroff, CB., 2000). Low basal levels of cortisol and an increase in stress reactivity have been associated with a sensitized HPA axis (Gutman & Nemeroff, 2003). Replicating the study with a comparison group with PTSD would help determine the possible differences between the cortisol profiles associated with both diagnoses. However, given the similarity in cortisol profiles, the putative mechanism of action may be similar. Indeed, it has previously been shown that, when exposed to consistently high levels of cortisol, the CNS becomes sensitized to threatening stimuli, which leads to a stronger response elicited by weaker triggers; this has been shown to result from both adult trauma and from chronic early maltreatment (Gutman & Nemeroff, 2003). Alternatively, it has been proposed that HPA dysregulation in PTSD is linked to a low cortical response to traumatic events, followed by decreased cortical baseline levels. This would lead to an increase in

glucocorticoid receptor density and responsivity, ultimately leading to an increased negative feedback and HPA sensitization (de Kloet et al., 2006) – it is possible that a similar mechanism of action may explain our results, and that more severe childhood trauma sensitizes the HPA axis of psychotic patients.

Our results fit very well within a recent theoretical model of psychosis. In their traumagenic neurodevelopmental model, Read and colleagues proposed that exposure to traumatic events during the development of the brain may have a detrimental impact on the maturation of the central nervous stress system, which could be a causal risk factor for psychotic disorders, even in the absence of PTSD (J. Read et al., 2001). Clearly our results support the traumagenic model, showing that, at the very least, there may be a subgroup of psychotic patients that have a different psychobiological profile, characterized by HPA abnormalities associated with early maltreatment. Separating the influence of pure genetics and the influence of environmental factors on the diathesis of psychotic disorders seems critical to clarifying current models of psychosis – a complete model would need to go beyond individual risk factors, and include interactions between genetic and environmental variables, such as childhood trauma.

Recognition that childhood maltreatment may be a causal risk factor for psychotic disorders has profound clinical implications. If we know that the presence of different risk factors produces different psychobiological profiles within a diagnostic category, then etiology should have an impact on treatment decisions. At the pharmacological level, it may be important to consider the impact of antipsychotics on the HPA axis. It is possible that pharmacological interventions aimed at regulating the HPA axis have an impact on treatment response in psychotic patients with childhood trauma. At the psychosocial level, specific therapies addressing childhood maltreatments should be offered; anecdotal evidence suggests that psychotherapies tailored to address trauma in schizophrenic patients who do not respond well to antipsychotics may help relieve the psychotic symptoms (Waldfogel & Mueser, 1988). Of course, within a framework where treatment differs depending on the etiological profile of the presenting illness, presence of childhood trauma should be considered in conjunction with other risk factors.

In light of our results, early maltreatment appears to be a significant predictor of a dysregulated HPA axis in adults diagnosed with a psychotic disorder. This supports the idea that distal environmental putative risk factors for psychotic disorders can help explain the heterogeneity found within that diagnostic category. Clearly, childhood maltreatment should be evaluated when the psychobiological profiles of psychotic patients are investigated.

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APPENDIX 1

Table 1

Winsorized Values – Old and New values – Diurnal Cortisol

Subject ID	Time point	Mean	Standard Deviation	Old value	New value
10008	6	.099	.126	.65	.29
10008	7	.345	.526	.81	.50
29999	3	.278	.207	.93	.79
9901	3	.278	.207	.68	.60

Table 2

Winsorized Values – Old and New values – Reactive Cortisol

Subject ID	Time point	Mean	Standard Deviation	Old value	New value
9610	2	.193	.174	0.59	0.55
9610	6	.247	.199	0.70	0.66
9649	3	.159	.121	0.60	0.45
10005	4	.257	.307	0.77	0.53
10006	8	.216	.236	0.91	0.60
10011	2	.193	.174	0.73	0.72
10011	4	.257	.307	1.42	0.60
10014	8	.216	.236	0.85	0.55

Table 3

Winsorized Values – Old and New value – Childhood Trauma

Subject ID	Mean	Standard Deviation	Old value	New value
10009	43.60	12.61	91	72

APPENDIX 2

Table 1

Model Summary for the Area Under the Curve for Morning Cortisol ground – Men only

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.16	0.03	-0.09	7.05	0.03	0.22	2.00	17.00	0.81
2	0.62	0.38	0.27	5.79	0.36	9.22	1.00	16.00	0.01
3	0.62	0.39	0.22	5.95	0.01	0.16	1.00	15.00	0.69

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 2

ANOVA Table the Area Under the Curve for Morning Cortisol ground – Men only

Model		Sum of Squares	df	Mean Square	F	p-value
1	Regression	21.73	2.00	10.87	0.22	0.81
	Residual	844.81	17.00	49.69		
	Total	866.55	19.00			
2	Regression	330.55	3.00	110.18	3.29	0.05
	Residual	536.00	16.00	33.50		
	Total	866.55	19.00			
3	Regression	336.24	4.00	84.06	2.38	0.10
	Residual	530.31	15.00	35.35		
	Total	866.55	19.00			

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 3

Childhood trauma and Area Under the Curve for Morning Cortisol ground – Men only

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	11.30	9.35		1.21	0.24
	Age	0.02	0.20	0.03	0.11	0.92
	Dysphoria	0.47	0.71	0.16	0.66	0.52
2	Constant	29.82	9.80		3.04	0.01
	Age	0.01	0.16	0.02	0.09	0.93
	Dysphoria	0.04	0.60	0.01	0.06	0.95
	Total Trauma	-0.35	0.12	-0.62	-3.04	0.01
2	Constant	34.88	16.14		2.16	0.05
	Age	0.01	0.17	0.01	0.06	0.96
	Dysphoria	-0.72	1.98	-0.25	-0.36	0.72
	Total Trauma	-0.48	0.33	-0.83	-1.45	0.17
	Trauma X Dysphoria	0.02	0.05	0.31	0.40	0.69

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 4

Model Summary for the Area Under the Curve for Morning Cortisol increase – Men only

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.32	0.10	0.00	3.92	0.10	0.97	2.00	17.00	0.40
2	0.33	0.11	-0.06	4.03	0.01	0.10	1.00	16.00	0.76
3	0.33	0.11	-0.13	4.15	0.00	0.02	1.00	15.00	0.88

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 5

ANOVA Table the Area Under the Curve for Morning Cortisol increase – Men only

Model		Sum of Squares	df	Mean Square	F	p-value
1	Regression	29.68	2.00	14.84	0.97	0.40
	Residual	260.84	17.00	15.34		
	Total	290.52	19.00			
2	Regression	31.27	3.00	10.42	0.64	0.60
	Residual	259.25	16.00	16.20		
	Total	290.52	19.00			
3	Regression	31.69	4.00	7.92	0.46	0.76
	Residual	258.84	15.00	17.26		
	Total	290.52	19.00			

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 6

Childhood trauma and Area Under the Curve for Morning Cortisol increase– Men only

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	5.64	5.20		1.08	0.29
	Age	-0.14	0.11	-0.31	-1.31	0.21
	Dysphoria	0.03	0.40	0.02	0.08	0.94
2	Constant	4.31	6.82		0.63	0.54
	Age	-0.14	0.11	-0.31	-1.27	0.22
	Dysphoria	0.06	0.42	0.04	0.15	0.88
	Total Trauma	0.03	0.08	0.08	0.31	0.76
2	Constant	2.95	11.28		0.26	0.80
	Age	-0.14	0.12	-0.31	-1.22	0.24
	Dysphoria	0.27	1.39	0.16	0.19	0.85
	Total Trauma	0.06	0.23	0.18	0.25	0.80
	Trauma X Dysphoria	-0.01	0.03	-0.14	-0.15	0.88

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 6

Model Summary for the Area Under the curve for the 24-hour Integrated Cortisol – Men only

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.16	0.03	-0.09	0.05	0.03	0.23	2.00	17.00	0.80
2	0.44	0.20	0.05	0.05	0.17	3.41	1.00	16.00	0.08
3	0.45	0.21	-0.01	0.05	0.01	0.17	1.00	15.00	0.68

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 7

ANOVA Table for the Area Under the curve for 24-hour Integrated Cortisol – Men only

Model		Sum of Squares	df	Mean Square	F	p-value
1	Regression	0.00	2.00	0.00	0.23	0.80
	Residual	0.05	17.00	0.00		
	Total	0.05	19.00			
2	Regression	0.01	3.00	0.00	1.31	0.31
	Residual	0.04	16.00	0.00		
	Total	0.05	19.00			
3	Regression	0.01	4.00	0.00	0.98	0.45
	Residual	0.04	15.00	0.00		
	Total	0.05	19.00			

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

Table 8

Childhood trauma and Area Under the Curve 24-hour Integrated Cortisol – Men only

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	Constant	0.14	0.07		2.08	0.05
	Age	0.00	0.00	0.09	0.34	0.73
	Dysphoria	0.00	0.01	-0.12	-0.47	0.65
2	Constant	0.24	0.08		2.89	0.01
	Age	0.00	0.00	0.08	0.34	0.74
	Dysphoria	0.00	0.01	-0.22	-0.92	0.37
	Total Trauma	0.00	0.00	-0.43	-1.85	0.08
2	Constant	0.28	0.14		2.08	0.06
	Age	0.00	0.00	0.07	0.30	0.77
	Dysphoria	-0.01	0.02	-0.53	-0.67	0.51
	Total Trauma	0.00	0.00	-0.68	-1.04	0.31
	Trauma X Dysphoria	0.00	0.00	0.36	0.41	0.68

Model 1: constant, dysphoria, age

Model 2: constant, dysphoria, Age, total trauma

Model 3: constant, dysphoria, Age, total trauma, total trauma X dysphoria

PATIENT INFORMATION AND CONSENT FORM

Title of Study:
Life Events and Schizophrenia

Principal Investigator:
Suzanne King, Ph.D.

Co-Investigators:
Alain Brunet, PhD
Serge Beaulieu, MD, PhD
Trino Baptista, MD
Jacques-Bruno Debruille, MD,
Claire-Dominique Walker, PhD

Graduate Student:
Darren Holowka, BA (McGill University)

Contact:
Douglas Hospital – Psychosocial Research Division
6875 LaSalle Blvd. Verdun, QC
(514) 761-6131 x.3444

You and your family have already participated in the study entitled "_____". We thank you again for your participation.

Purpose of the Study

A number of studies have found that certain stressful events may be related to mental health problems. We hope that the study we are presently conducting will allow us to gain a better understanding of what types of events that may have occurred during your life may explain the experiences and problems you have had.

Your Participation in the Study

For the purposes of this study, we would like to meet with you and have you participate in some tests. Before we meet for the interview and testing session, we will ask you to take 7 samples of saliva on the day before we meet. We will give you the necessary containers and explain how this is done. We will lend you a pager for the day, which will "beep" you every time you must take a sample.

The interview will take about 1 hour to complete. The questions you will be asked are about stressful events that may have happened to you during your life. Following a break, we will attach some wires to your arm and record the electrical activity on your skin in response to different situations. This should take about 2 hours. At different points during this test we will also ask you to provide 4 saliva samples, in the same way as you did the day before. After this, you will be fitted with a cap (similar to a bathing cap) that has wires attached to it, which measure the electrical activity of your brain. Once the cap is on, we will ask you to look at a series of pictures on a computer screen. This part of the study should take about 3 hours. Thus, the whole day of interview and testing should take about 6 hours in total.

Compensation

You will receive compensation of $70 for your participation after the interview and testing is completed, or in the case that it is not completed, you will receive a compensation of $10 for each completed hour.

Risks and Benefits of the Study

You understand that there are no risks associated with the study, except for possible emotional discomfort associated with certain questions. You have the right to refuse to answer any questions you prefer not to answer. Placing of the cap on your head should not hurt at all, but it may be slightly uncomfortable. Although there is no direct benefit for participating in this study, you understand that the information that you provide is important for giving us a better understanding of the problems that you have had.

You know that your decision to participate or to not participate in this project, or to withdraw from the study at any time, will have no consequence on the clinical services that you, or your family, may receive.

Confidentiality

This project is confidential, which means that only the persons associated with the study will have access to your information, unless otherwise specified by law, and all information will be kept in a drawer of a locked filing cabinet. All data pertaining to subjects will not be identified by their name, but with a code number. Finally, you understand that any publications of the study will not identify any particular individual, but will only contain reports on groups of individuals.

PARTICIPANT'S CONSENT

I have read and understood the description of my involvement in this project and have had opportunities to ask questions.

I give permission to the researchers of this project to interview me about the types of events that may have happened in the past that could explain the kinds of problems that I have experienced. I understand that the questions I will be asked may be sensitive in nature, but I can refuse to answer any questions or end the interview at any time.

I also give my permission for the investigators to use the information I gave during the study entitled "_____" for the purpose of answering these new questions.

I have received a copy of this form. I understand that if I have any further questions, I can contact the researchers identified on the first page at 761-6131 or at the address at the bottom of the first page. I may also contact the Douglas Hospital Ombudsman if I have any questions about my rights as a patient or as a research subject at 761-6131 local 3287.

Name (please print) _____

Signature _____ Date _____

Witness _____

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT DU PATIENT

Titre de la recherche:
Etude sur les événements de vie et la schizophrénie

Investigateur principal:
Suzanne King, Ph.D.

Co-investigateurs:
Alain Brunet, PhD
Serge Beaulieu, MD, PhD
Trino Baptista, MD
Jacques-Bruno Debruille, MD,
Claire-Dominique Walker, PhD

Étudiant gradué:
Darren Holowka, B.A. (Université McGill)

Contact:
Centre de Recherche de l'Hôpital Douglas
Division psychosociale
6875 Boul. Lasalle, Verdun, QC
tel : (514) 761-6131 poste 3444

Vous, ainsi que certains membres de votre famille, avez déjà participé dans l'étude intitulée, "_____". Nous tenons à vous remercier une fois de plus pour votre participation dans cette étude.

Objectif de l'étude

Plusieurs études ont démontré que certains événements stressants peuvent être associés à des troubles graves de la santé mentale. Nous espérons que l'étude que nous dirigeons présentement nous permettra de mieux comprendre quels types d'événements auraient pu survenir au courant de votre vie qui peuvent expliquer les expériences et les problèmes que vous avez vécus.

Votre participation à l'étude

Nous aimerions vous rencontrer pour compléter cette étude. Avant de se rencontrer, on vous demandera de fournir 7 échantillons de salive. On vous donnera les contenants requis et vous expliquera comment ça se fait. On vous pretera une paguette pour la journée qui vous avisera à chaque fois qu'on vous demande de prendre un échanitillon.

L'entrevue durera environ 6 heures et comportera plusieurs questionnaires et testes. Le premier questionnaire portera sur le début et la fréquence de certaines expériences que avez peut-être déjà vécues. Après une pause, on attachera des fils à votre bras pour enregistrer l'activité electrique sur votre peau pour differentes situations. Après cette partie, vous regarderez des images sur un ecran et on vous demanera de prendre des décisions à propos des images. Pendant la tâche, l'activité cérébrale sera enrégistrée; pour cela un(e) assistant(e) de recherche vous posera un casque élastique sur la tête.

Compensation pour votre participation

En guise de récompense, une somme de 70$ vous sera remise à la fin de l'entrevue. Par contre, dans le cas où les évaluations ne seraient pas complétées, vous recevrez un somme 10$ en guise de dédommagement pour chaque heure d'entrevue complétée.

Risques et bénéfices de l'étude

Bien qu'il n'y ait pas d'avantages directement reliés à cette étude, l'information que vous nous fournirez est très importante et nous aidera à mieux comprendre les problèmes que vous avez peut-être eu. Le seul risque, minime, qui pourrait être associé à cette entrevue est que vous puissiez vous sentir troublé(e) ou perturbé(e) en parlant des moments difficiles que vous auriez pu avoir vécus. Vous avez le droit de refuser de répondre aux questions auxquelles vous préférez ne pas répondre. La pose du casque n'est pas doulureuse, mais elle peut être un peu inconfortable. Les enregistrements electriques ne comportent aucun risque, sauf celui d'une légère réaction allergique locale qui est très rare et qui n'a aucune conséquence sur la santé. Votre décision de participer ou de refuser de participer dans cette étude ou de vous retirer de l'étude à tout moment n'aura aucune conséquence sur les services cliniques que vous ou votre famille pouvez recevoir.

Confidentialité

Ce projet est confidentiel, ce qui veut dire que seules les personnes travaillant sur l'étude pourront avoir accès à votre dossier, sauf si spécifié par la loi. Les informations que vous fournirez seront gardées sous-clef. Toutes les donnés seront identifiées non par le nom du patient, mais par un numéro d'identité. Les publications issues de cette étude ne révéleront pas les noms des personnes qui y auront participé, elles ne s'intéresseront qu'aux groupes de personnes.

CONSENTEMENT DU PATIENT

J'ai lu et j'ai compris les conditions de ma participation dans cette étude et j'ai eu l'occasion de poser des questions.

Je donne ma permission aux chercheurs de me poser des questions ayant trait à cette recherche. Je comprends que les questions qui me seront posées peuvent être délicates, mais je peux refuser de répondre à n'importe quelle question et je peux même décider de mettre fin à l'entretien à n'importe quel moment.

Je donne ma permission aussi d'utiliser les informations me conçernant, acquis pendant l'étude intitulée "_____" à fins de repondre à ces nouveaux questions.

J'ai reçu une copie de ce formulaire. Si j'ai des questions, je peux téléphoner aux chercheurs identifiés sur la première page au 761-6131 ou à l'adresse indiquée au bas de la première feuille. Je peux également téléphoner à l'ombudsman de l'Hôpital Douglas au 761-6131 poste 3287 si j'ai des questions au sujet de mes droits en tant que sujet de recherche.

Nom (en lettres moulées s.v.p.) _____

Signature _____ Date _____

Témoin _____

Brief Psychiatric Rating Scale (Version 4.0)

Name/ID # : _____ Date: _____ Interviewer: _____

NA	1	2	3	4	5	6	7
Not Assessed	Not present	Very Mild	Mild	Moderate	Moderately Severe	Severe	Extremely Severe

Rate items 1-14 on the basis of the patient's self-report during the interview (N.B. Items 7, 12 and 13 are also rated on basis of observed behaviour)

1.	Somatic Concern	1	2	3	4	5	6	7
2.	Anxiety	1	2	3	4	5	6	7
3.	Depression	1	2	3	4	5	6	7
4.	Suicidality	1	2	3	4	5	6	7
5.	Guilt	1	2	3	4	5	6	7
6.	Hostility	1	2	3	4	5	6	7
7.	Elevated Mood	1	2	3	4	5	6	7
8.	Grandiosity	1	2	3	4	5	6	7
9.	Suspiciousness	1	2	3	4	5	6	7
10.	Hallucinations	1	2	3	4	5	6	7
11.	Unusual Thought	1	2	3	4	5	6	7
12.	Bizarre Behavior	1	2	3	4	5	6	7
13.	Self-neglect	1	2	3	4	5	6	7
14.	Disorientation	1	2	3	4	5	6	7

Rate items 15-24 on the basis of observed behaviour or speech of the patient during the interview.

15.	Concept. Disorganization	1	2	3	4	5	6	7
16.	Blunted Affect	1	2	3	4	5	6	7
17.	Emotional Withdrawal	1	2	3	4	5	6	7
18.	Motor Retardation	1	2	3	4	5	6	7
19.	Tension	1	2	3	4	5	6	7
20.	Uncooperativeness	1	2	3	4	5	6	7
21.	Excitement	1	2	3	4	5	6	7
22.	Distractibility	1	2	3	4	5	6	7
23.	Motor Hyperactivity	1	2	3	4	5	6	7
24.	Mannerisms and Posturing	1	2	3	4	5	6	7

Confidence in assessment :
_____ 1 = Not at all - 5 = Very Confident

Explain here if validity of assessment is questionable :
_____ Symptoms possibly drug-induced
_____ Underreported due to lack of rapport
_____ Underreported due to negative symptoms
_____ Patient uncooperative
_____ Difficulty to assess due to formal thought disorder
_____ Other _____

CTQ

Date (dd/mm/yy): _____ ID: _____

Interviewer: _____

When I was growing up...	*Never true*	*Rarely true*	*Some-times true*	*Often true*	*Very often true*
PN1. I didn't have enough to eat	•	•	•	•	•
PN2. I knew that there was someone to take care of me an protect me	•	•	•	•	•
EA3. People in my family called me things like "stupid", "lazy", or "ugly"	•	•	•	•	•
PN4. My parents were too drunk or high to take care of the family	•	•	•	•	•
EN5. There was someone in my family who helped me feel that I was important or special	•	•	•	•	•
PN6. I had to wear dirty clothes	•	•	•	•	•
EN7. I felt loved	•	•	•	•	•
EA8. I thought that my parents wished I had never been born	•	•	•	•	•
PA9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital	•	•	•	•	•
MD10. There was nothing that I wanted to change about my family	•	•	•	•	•
PA11. People in my family hit me so hard that it left me with bruises or marks	•	•	•	•	•
PA12. I was punished with a belt, a board, a cord, or some other hard object	•	•	•	•	•
EN13. People in my family looked out for each other	•	•	•	•	•
EA14. People in my family said hurtful or insulting things	•	•	•	•	•
PA15. I believe that I was physically abused	•	•	•	•	•
MD16. I had the perfect childhood	•	•	•	•	•
PA17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor	•	•	•	•	•
EA18. I felt that someone in my family hated me	•	•	•	•	•

When I was growing up...	*Never true*	*Rarely true*	*Some-times true*	*Often true*	*Very often true*
EN19. People in my family felt close to each other	•	•	•	•	•
SA20. Someone tried to touch me in a sexual way, or tried to make me touch them	•	•	•	•	•
SA21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them	•	•	•	•	•
MD22. I had the best family in the world	•	•	•	•	•
SA23. Someone tried to make me do sexual things or watch sexual things	•	•	•	•	•
SA24. Someone molested me	•	•	•	•	•
EA25. I believe that I was emotionally abused	•	•	•	•	•
PN26. There was someone to take me to the doctor if I needed it	•	•	•	•	•
SA27. I believe that I was sexually abused	•	•	•	•	•
EN28. My family was a source of strength and support	•	•	•	•	•
WV33. I saw people in my family get hit or beaten	•	•	•	•	•
FP43. I had serious money problems	•	•	•	•	•
FP44. My family had serious money problems	•	•	•	•	•
H45. I was living on the streets by the time I was a teenager or younger	•	•	•	•	•
EPA48. People in my family argued or fought with each other	•	•	•	•	•
EPA49. I had to protect myself from someone in my family by fighting, hiding, or running away	•	•	•	•	•
PA51. The punishments I received seemed cruel	•	•	•	•	•
SS46. There was someone outside the family (e.g. teacher or neighbor) who was like a parent to me	•	•	•	•	•
SS47. There was someone in my family whom I could talk to about my problems	•	•	•	•	•
PA50 The punishments I received seemed fair	•	•	•	•	•

When I was growing up...	*Never true*	*True*
SA52. I had sex with an adult or with someone who was at least 5 years older than me	•	•
PN53. People in my family had secrets that I wasn't supposed to share with anyone	•	•
V34. I was robbed or mugged or attacked	•	•
WV35. I saw someone get robbed or mugged or attacked	•	•
WV36. I saw someone get hurt or killed	•	•
LS29. My parents separated or divorced	•	•
LS30. I lived in a group home or foster home or with a relative	•	•
LS31. My parents or a relative died suddenly/ committed suicide	•	•
LS32. A close friend died suddenly/committed suicide	•	•
ND37. I was in a serious natural disaster (earthquake, hurricane, fire, flood)	•	•
AC38. I was in a serious accident (in a car, at work, or somewhere else)	•	•
AC39. A close family member was in a serious accident (in a car, at work, or somewhere else)	•	•
AC40. I saw a serious accident (e.g. car accident, work accident)	•	•
J41. One of my parents spent time in jail	•	•
J42. I spent time in jail	•	•
C54. I had an abortion or miscarriage (lost my baby)	•	•
C55. I was separated from my child against my will	•	•

1. HAVE YOU EVER EXPERIENCED ANY OTHER STRESSFUL SITUATION? ___
[IF YES], WHAT WAS IT? _____

_____

_____

2. OF ALL THE STRESSFUL EVENTS EXPERIENCED, WHICH ONES HAD THE GREATEST IMPACT ON YOU?

WORST EVENT? _____

_____

SECOND WORST EVENT? _____

_____

THIRD WORST EVENT? _____

_____