Review

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A systematic review of hypothalamic–pituitary–adrenal axis function in schizophrenia: implications for mortality

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Abstract

There is convincing evidence that environmental stress plays a significant role in modifying both mental and physical health. The biological mechanisms linking stress to ill health are not fully understood, but significant evidence points to a central role of the stress axes; the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. Together these two systems link the brain and the body and are crucial in maintaining homeostasis as well as improving an organism's survival chances in the face of environmental challenge. There is evidence of altered HPA axis function in people with a range of mental disorders, and this may in part explain the poor physical health of people with psychotic, mood and anxiety disorders. This paper systematically reviews HPA axis function in people with schizophrenia and relates this to the pattern of physical health seen in this disease. In summary, the evidence suggests people with schizophrenia can experience both hyper- and hypo-function of the HPA axis. It is likely that this contributes to the pattern of poor physical health and premature mortality suffered by people with schizophrenia, in particular the high rates of cardiovascular and metabolic disturbance.

Keywords

Coronary heart disease, cortisol, hypothalamic–pituitary–adrenal axis, metabolic syndrome, mortality, schizophrenia

Introduction

Stress has a powerful effect on both the brain and the body (McEwen, 1998) and has a significant role in the development and course of mental and physical illness (Burcusa and Iacono, 2007; Cohen et al., 2007; Kendler et al., 1999; McEwen and Stellar, 1993; Walker and Diforio, 1997). Evidence has accumulated that chronic stress has significant effects on both brain structure and function (McEwen and Gianaros, 2010; Pruessner et al., 2010; Sapolsky, 2003) and on whole body systems (Rosmond, 2005), cumulating in disease and increased mortality. Stress, which can be both physical and psychological, has been defined as a state where homeostasis is threatened or perceived to be threatened, and animals have developed a range of behavioural and physiological responses in order to maintain homeostasis in situations of stress (Chrousos and Gold, 1992). The brain is the central organ in the adaptation to stress, since it determines what is threatening or benign. The biological response to stress is then mediated through the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), which invoke a number of adaptive behavioural and physiological changes that enhance survival of the individual in the face of stress. Together the stress axes influence many bodily processes, including cardiovascular function and the provision of energy substrates, and that they are tightly regulated suggests that any over or under activity may be detrimental to health (Chrousos and Gold, 1992). For detailed reviews of the function of the stress axes and the central role of the brain the reader is referred to Tsigos and Chrousos (2002) and McEwen and Gianaros (2010).

Over recent decades science has begun to unravel the biological mechanisms by which stress can harm the brain and body, aiding our understanding of the aetiology of both mental and physical ill health. Since the adaptive response to stress is designed to increase survival, it follows that a dysfunctional stress response (over or underactivity) may be damaging to an individual. One way of considering this is the concept of allostatic load. The adaptive response has also been termed allostasis (Sterling and Eyer, 1988), while allostatic load represents the wear and tear the body experiences when repeated allostatic responses are activated (or not)

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during stressful situations (McEwen and Stellar, 1993). Allostatic load can occur in a number of ways, such as exposure to frequent or chronic stressors, invoking a frequent or chronic stress cascade. For example, frequent increases in blood pressure may accelerate atherosclerosis or trigger myocardial infarction in susceptible individuals. (McEwen, 1998). Failure to deactivate the stress response within a dysfunctional stress system could lead to over exposure to the effects of glucocorticoids and/or catecholamines. This can result in the development of central obesity, type 2 diabetes, hypertension and cardiovascular disease (Rosmond, 2005). The result of overexposure to cortisol is demonstrated in Cushing's syndrome, a disorder characterized by chronic hypercortisolaemia and the features of the metabolic syndrome (Shibli-Rahhal et al., 2006). The absence of an appropriate stress response or hypofunction of the HPA axis can also be damaging (Heim et al., 2000; Raison and Miller, 2003). For example, a lack of the usual anti-inflammatory cortisol response to stress may allow prolonged exposure to SNS-stimulated immune and inflammatory function, causing disease. Stress may also have indirect effects on physical health, as exposure to psychological stress may modify an individual's health behaviours and increase risk for the development of disease. For example, people confronted with chronic stress in daily life may engage in unhealthy behaviours such as smoking, alcohol and substance misuse and poor dietary choices; they may also be less likely to engage in physical activity (Hemingway and Marmot, 1999; Oliver et al., 2000; Steptoe et al., 1996).

There is good evidence that the HPA and SNS axes are dysfunctional in a range of mental disorders (Brown et al., 2009; Fujibayashi et al., 2009; Meewisse et al., 2007; Walker et al., 2008; Watson and Mackin, 2006), and this dysfunction therefore provides a possible mechanism for the common co-existence of poor mental and physical health (Golden, 2007; Goldston and Baillie, 2008; Mondelli and Pariante, 2008; Ryan and Thakore, 2002). The evidence for HPA dysfunction in schizophrenia has been reviewed in the context of the diathesis–stress model of schizophrenia (Walker and Diforio, 1997; Walker et al., 2008), but to date this evidence has not been systematically reviewed.

Thus, the aim of this paper is twofold:

To systematically review the evidence for HPA axis dysfunction in patients with schizophrenia

To assess whether any evidenced dysfunction is contributing to the poor physical health of people with schizophrenia.

Methods

Determining HPA axis function in humans is challenging. Markers of basal as well as stimulated HPA activity are required in order to fully reveal and understand the mechanisms (Kudielka and Wust, 2010). Therefore controlled studies that measured one or more of the following variables or utilized the HPA axis probes listed below were systematically reviewed:

Levels of basal cortisol, adrenocorticotropin hormone (ACTH) or corticotropin-releasing hormone (CRH) as a single measure or over time

CRH test

Dexamethasone (DEX)/CRH test

Effects of psychological stressors on HPA function

Dexamethasone suppression test (DST).

The search was restricted to peer-reviewed journals and sought published articles that measured the above variables in adult (aged > 18 years), schizophrenia patients. The OVID databases of Medline, Embase and Psychinfo were searched from the earliest time point to March 2010 by a qualified information scientist. Search terms included hypothalamo–hypophyseal system, hydrocortisone, adrenocorticotropin hormone, corticotropin-releasing hormone, all combined with schizophrenia. Abstracts were reviewed by one author (AB) and the full, original article obtained for any study that examined the areas of interest. Studies were examined for any potential cohort overlap with previous publications by the same group. Where cohorts overlapped, only the larger study was included. Authors were contacted if overlap was unclear. The reference list of all relevant articles and review articles was also searched for any additional studies not identified during the OVID searches. Following these searches, studies were included in the systematic review only if they met the following inclusion criteria:

Data published from 1980 onwards on the basis that studies reported before this date did not use control groups for basal measures and most also utilized outdated assay methods to detect levels of HPA secretories which may now be considered inaccurate

Written in English

Patients diagnosed with schizophrenia using structured diagnostic interviews such as DSM or RDC criteria

Schizophrenia diagnosed in at least 90% of the reported psychiatric cohort. If other diagnostic categories were included in the cohort (e.g. major depression or schizophreniform disorder) and accounted for more than 10% of the total sample, results from the schizophrenia cohort reported separately

The assay used to measure physiological outcomes was reported

For studies of basal HPA functioning, blood, cerebrospinal fluid (CSF), salivary or urinary measures taken as a single sample or at multiple time points and compared with non-psychiatric controls. The difference between schizophrenia patients and controls was reported

Minimum of 10 schizophrenia patients in studies using the DST. The 1.0 mg DST was used with a post-DEX cortisol cut-off for non-suppression of 138 nmol/L (5 ug/dL). Studies using only one time point for measurement of post-DEX cortisol before 16 : 00 were excluded. The rate of non-suppression must have been reported. Studies utilizing the DST did not require a control group since the rate of non-suppression of cortisol during this test in the general population is well documented

Studies measuring the response of the HPA axis to psychological stress used a psychological stressor with the ability to produce a measurable stress response as assessed by the cortisol, ACTH or CRH response in a non-psychiatric control group.

The initial search identified 1002 articles. After reviewing the abstract, 786 articles were discarded either because they were published pre-1980, did not describe the subject matter of interest, were not written in English or were review articles with no original data. The full published article was obtained for the remaining 216 articles. Of these, 160 met the inclusion criteria and were included in the systematic review. Fifty-six articles were rejected as follows:

Schizophrenia patients less than 90% of the psychiatric cohort or data for schizophrenia patients were not reported separately ($n = 16$)
Fewer than 10 patients in DST studies ($n = 13$)
Inadequate control group ($n = 8$)
Results for schizophrenia patients not specifically reported ($n = 6$)
Overlap with a previously reported cohort ($n = 5$)
Studies did not use the defined DST method ($n = 5$)
Inadequate description of study methods ($n = 3$).

Data were extracted from the included studies and tabulated to aid interpretation. All extracted data were verified during a data integrity review undertaken by a third person (see Acknowledgements). Basic analysis was performed and conclusions on HPA functioning in schizophrenia patients were drawn. Any evidenced dysfunction was evaluated with respect to its possible effects on physical disease and mortality by performing a brief and selected review of the evidence for the role of HPA axis dysfunction in the aetiology of physical disease.

Results

Basal cortisol

In total, 77 studies measuring basal cortisol in 1928 schizophrenia patients and 1699 controls met the stated inclusion criteria (Tables 1, 2 and 3; five studies appear in more than one table, either because they reported on more than one cohort of schizophrenia patients or because 24-h cortisol levels were similar for schizophrenia patients and controls but significant differences were found at a single time point). These studies were heterogeneous in their methodology and outcomes, making interpretation of the results complex. Variations in methods included the time of cortisol measurement and whether patients were medicated or drug free, symptomatic or stable.

Analysis of all 77 studies combined provided evidence that mean basal cortisol levels are elevated in some but not all schizophrenia patients. Mean basal cortisol was statistically significantly elevated in schizophrenia patients compared with controls (area under the curve (AUC) or at a single time point) in 34/77 (44.2%) studies. Basal cortisol was not significantly different between schizophrenia patients and controls in 44/77 (57.1%) studies, and basal cortisol was significantly lower in schizophrenia patients than in controls in 4/77 (5.2%) studies. Elevated basal cortisol was reported in studies including acutely psychotic patients, for example Albus et al. (1982), Gil-Ad et al. (1986), Muck-Seler et al. (2004) and Whalley et al. (1989), in patients described as more stable as reported by Breier and Buchanan (1992), Gallagher et al. (2007), Yilmaz et al. (2007), and in patients with prominent negative symptoms and an absence of positive symptoms as demonstrated in Altamura et al. (1989) and Shirayama et al. (2002). These studies demonstrate that elevated cortisol can be present in schizophrenia patients at different phases of the illness and with different levels and types of symptoms.

Studies measuring 24-h cortisol or cortisol measured over multiple time points

As cortisol is secreted in a circadian rhythm over a 24-h period, studies that measured 24-h cortisol level or measured cortisol over several time points spanning at least 3 h within a 24-h period were examined separately. This analysis would indicate if differences in cortisol are sustained over time rather than at a single time point, and might also detect differences in cortisol secretion at different times of the day, indicating disruption to the normal circadian rhythm.

In total, 18 studies including 421 schizophrenia patients measured basal cortisol over at least a 3-h time interval. Four of these studies found evidence of increased cortisol in schizophrenia patients that was not sustained, i.e. a difference in cortisol level was found at only one time point measured. Christie et al. (1986) and Whalley et al. (1985) found elevated afternoon but not morning or evening cortisol in schizophrenia patients recently admitted to hospital ($p < 0.05$ and $p < 0.02$, respectively). The study reported by van Cauter et al. (1991) found no difference in 24-h cortisol in drug-free, recently hospitalized, acutely ill patients but the early sleep mean (00:00–04:00) was significantly higher in schizophrenia patients than in controls. Likewise the study by Jiang and Wang (1998) found no difference in mean 24-h cortisol in medicated, acutely ill inpatients, but found a significantly higher cortisol level in schizophrenia patients between 02:00 and 03:00. Seven of the 18 (38.9%) studies found evidence for sustained elevation or elevation of cortisol at more than one time point in schizophrenia patients. Morphy et al. (1985) found elevated cortisol in acutely ill schizophrenia patients relative to controls at both 08:00 ($p < 0.01$) and 16:00 ($p < 0.001$), as did Altamura et al. (1989), 08:00 ($p < 0.05$) and 16:00 ($p < 0.001$), in patients with prominent positive or negative symptoms. Whalley et al. (1989) reported significantly elevated cortisol at morning, afternoon and evening measures in drug-free, acutely psychotic patients ($p < 0.05$). Gil-Ad et al. (1986) found evidence of elevated cortisol when measured at 3-h intervals from 07:00–22:00 in acutely psychotic schizophrenia patients. Levels were significantly elevated compared with controls at 07:00, 10:00, 19:00 and 22:00 ($p < 0.05$) and at 13:00 ($p < 0.01$). Monteleone et al. (1992) reported a 16-h cortisol profile (AUC) that was significantly higher in moderately ill, chronic schizophrenia patients than in controls ($p < 0.001$). Two studies measured cortisol between 13:00 and 16:00, a measure that strongly correlates with 24-h cortisol (Halbreich et al., 1982). Ryan et al. (2004b) reported significantly higher AUC cortisol in mildly ill, first-episode, drug-naive schizophrenia patients ($p < 0.01$), and Gallagher et al. (2007) reported afternoon cortisol to be significantly higher in symptomatically

Table 1. Studies finding basal cortisol significantly greater in schizophrenia patients versus controls

Study	SCH (*n*)	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	*p*-value and comments
Albus et al. (1982)	12	Drug free 4 weeks, acutely psychotic	Plasma cortisol time not stated	$p < 0.05$
Ferrier et al. (1982)	15	Drug free >1 year, chronic SCH, inpatients	Plasma cortisol 00.00	$p < 0.01$
Morphy et al. (1985)	18	FGA, newly admitted	Plasma cortisol 08.00 and 16.00	$p < 0.01$ & $p < 0.001$
Whalley et al. (1985)	13	Drug free 6 months, newly admitted	Plasma cortisol am, pm and evening	$p < 0.02$ pm only
Christie et al. (1986)	24	Drug free 3 months, acutely psychotic, admitted	Plasma cortisol am, pm and evening	$p < 0.05$ pm only
Gil-Ad et al. (1986)	10	Drug free 10 days, acutely psychotic	Plasma cortisol 07.00–22.00 (3 hourly)	$p < 0.05$ except 16.00
Altamura et al. (1989)	54	FGA, inpatients	Plasma cortisol 08.00 and 16.00	$p < 0.05$ & $p < 0.001$ −ve SCH > + SCH 16.00 $p < 0.01$
Whalley et al. (1989)	26	Drug free 3 months, acutely psychotic, admitted	Plasma cortisol am, pm and evening	$p < 0.05$ am, pm and evening
van Cauter et al. (1991)	9	Neuroleptic free 9 weeks, hospitalized, BPRS 43–79	24 hour plasma cortisol every 15 min	$p < 0.004$ (00.00–04.00) 24 hour mean cortisol SCH = CON
Breier and Buchanan (1992)	9	Drug free 8–77 days, stable, chronic outpatients	Plasma cortisol 09.00 on 2 days	$p = 0.04$ (day 1) SCH = CON (day 2)
Monteleone et al. (1992)	7	Drug free ≥3 weeks, outpatients, admitted for study. BPRS 41.1	Plasma cortisol 20.00–12.00 (16 hours)	$p < 0.0002$ (16 hour cortisol profile) $p < 0.001$ (cortisol AUC)
Lammers et al. (1995)	24	9 patients drug free, 7 FGA, 8 SGA. Mean BPRS 41	Plasma cortisol between 14.00–15.00	$p < 0.01$
Abel et al. (1996)	13	First-episode drug-naïve inpatients BPRS 39.2	Plasma cortisol between 08.00–09.00	$p = 0.0059$
Jiang and Wang (1998)	21	All patients receiving FGA. Inpatients. BPRS 48.3	24 hour plasma cortisol	$p < 0.01$ (02.00 and 03.00) AUC cortisol SCH = CON
Markianos et al. (1999)	31	FGA hospitalized poor treatment response BPRS 45.0	Plasma cortisol 09.00	$p = 0.001$
Monteleone et al. (1999)	16	Drug free, inpatients. 9/16 patients treatment resistant	Plasma cortisol 09.00–09.30	$p < 0.03$
Muck-Seler et al. (1999)	86	Drug free for 7 days. Admitted	Plasma cortisol 08.00	$p < 0.001$
Meltzer et al. (2001)	51	Drug free 7 days, hospitalized 58.8% treatment resistant. BPRS 28.7	Plasma cortisol 08.30–09.00	SCH > CON ($p = 0.003$)
Shirayama et al. (2002)	28	Neuroleptics. In and out patients with an absence of positive sx. Patients split into low ($n = 14$)and moderate negative sx groups ($n = 14$)	Plasma cortisol between 08.30–11.30	$p < 0.01$ (SCH moderate negative sx) SCH low negative sx = CON
Thakore et al. (2002)	15	Drug naive and drug free, mostly inpatients BPRS 22.6	Plasma cortisol 16.00	$p < 0.008$
Ryan et al. (2003)	26	First-episode drug-naive inpatients. BPRS 54.8	Plasma cortisol 08.00	$p < 0.0001$
Muck-Seler et al. (2004)	20	12 drug free for 8 weeks, 8 for 7 days. BPRS 58.5 CGI 5.2	Plasma cortisol 08.00	$p < 0.05$
Ryan et al. (2004a)	19	Hospitalized first episode drug naive. BPRS 32.1	Plasma cortisol 08.30	$p < 0.003$
Ryan et al. (2004b)	12	Hospitalized first episode drug naive. BPRS 36.7	Plasma cortisol 13.00–16.00	$p < 0.01$ (AUC 13.00–16.00)
Walsh et al. (2005)	10	Hospitalized first episode drug naive. BPRS 42.9	Plasma cortisol 13.00	$p < 0.02$
Zhang et al. (2005)	78	Drug free for 2 weeks. Treatment-resistant inpatients. Pre-treatment PANSS ~80, post-treatment PANSS ~63	Serum cortisol 07.00–09.00	$p < 0.01$ (pre and post treatment)

(continued)

Table 1. Continued

Study	SCH (*n*)	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	*p*-value and comments
Gallagher et al. (2007)	20	Antipsychotics, stable but symptomatic. BPRS 29.7	Plasma cortisol 13.00–16.00	$p = 0.003$ (13.00–16.00)
Popovic et al. (2007)	18	FGA, inpatients. PANSS 90.5	Plasma cortisol 08.00	$p < 0.05$ SCH = CON post SGA treatment
Ritsner et al. (2007)	43	Inpatients, FGA and SGA. PANSS 101.7	Plasma cortisol 08.00–09.00 assessed at baseline and after 2 and 4 weeks	$p < 0.001$ at all time points
Spelman et al. (2007)	38	First episode drug naive, hospitalized, BPRS 44.4	Plasma cortisol 08.30	$p < 0.001$
Venkatasubramanian et al. (2007)	44	All patients antipsychotic naive. Mean SAPS 30.7 and SANS 63.1	Plasma cortisol between 08.00–09.00	$p < 0.001$
Yilmaz et al. (2007)	66	All patients taking FGA. BPRS 17.89	Plasma cortisol between 08.30–11.30	$p < 0.05$
Kale et al. (2010)	31	Outpatient first episode drug naive. PANSS ~105	Plasma cortisol time not stated	$p < 0.05$
Venkatasubramanian et al. (2010)	33	Drug naive. SAPS 36.2, SANS 65.6	Plasma cortisol between 08.00–09.00	$p = 0.0002$

AUC, area under the curve; BPRS, brief psychiatric rating scale; CGI, clinical global impression; CON, controls; FGA, first generation antipsychotic; PANSS, positive and negative syndrome scale; SAPS, scale for the assessment of positive symptoms; SANS, scale for the assessment of negative symptoms; SCH, schizophrenia; SGA, second-generation antipsychotic; sx, symptoms.

Table 2. Studies finding basal cortisol not significantly different between schizophrenia patients and controls

Study	SCH (*n*)	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	Comments
Brophy et al. (1983)	13	Drug free for 2 months, acutely psychotic	Plasma cortisol at varying times	–
Stokes et al. (1984)	13	Drug free ≥9 days. Recently hospitalized chronic SCH	Plasma cortisol 08.30 and 22.00	–
Banki et al. (1985)	20	Drug free for 2 weeks. Recently hospitalized	Plasma cortisol 09.00–10.00	–
Gattaz et al. (1985)	15	Neuroleptic treated, admitted	CSF cortisol 09.00–10.00	–
Roy et al. (1986)	9	Acutely psychotic newly admitted chronic SCH, tested while drug free for 2 weeks and on fluphenazine	Plasma cortisol 20.00	No significant differences in drug-free or medicated patients
Whalley et al. (1986)	12	Long term neuroleptics, chronic but newly admitted	Single plasma cortisol 11.30–12.30	–
Wolkowitz et al. (1986)	8	Drug free for 4 weeks and medicated cohorts. Inpatients	Plasma cortisol 09.15 and 09.30	No significant differences with drug-free, medicated or controls
Zhou et al. (1987)	48	Drug free for 1 week. Inpatients	Plasma cortisol 23.00	–
Breier et al. (1988a)	10	Drug free for 3 weeks. Chronic course, admitted	Plasma cortisol 08.00–09.00	–
Breier et al. (1988b)	8	All receiving fluphenazine.	Plasma cortisol 09.00–10.00	–
Lerer et al. (1988)	10	Drug free for 4 weeks Chronically hospitalized with prominent negative symptoms but attenuated positive symptoms. Treatment resistant. BPRS 34.2	Plasma cortisol between 08.30 and 08.45 measured prior to fenfluramine or placebo challenge	Trend towards higher cortisol in SCH group on both placebo ($p = 0.1$) and fenfluramine challenge days ($p = 0.06$)
Davila et al. (1989)	11	FGA. Chronic and subchronic. Setting not stated.	Plasma cortisol 08.30 and 12.30	–
Fanget et al. (1989)	23	All receiving FGA. BPRS 60.3	Plasma cortisol 24.00 (midnight)	–
Wolkowitz et al. (1989)	16	Drug free for 3 weeks. Illness phase and setting not stated	Plasma cortisol 16.00	–
Nerozzi et al. (1990)	18	Drug free 3 months. 13 acute inpatients, five chronic outpatients	Plasma cortisol 08.00	–

(continued)

Table 2. Continued

Study	SCH (n)	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	Comments
Iqbal et al. (1991)	7	Drug free for 2 weeks. Chronic SCH inpatients ($n = 5$) and outpatients ($n = 2$)	Plasma cortisol 10.00	–
van Cauter (1991)	9	Neuroleptic free 9 weeks, hospitalized. BPRS 43–79	24-h plasma cortisol every 15 min	$p < 0.004$ (00.00–04.00) 24-h mean cortisol SCH = CON
Kathol et al. (1992)	5	Drug free for 2 weeks. Inpatients	Plasma cortisol 16.00	–
Risch et al. (1992)	32	Drug free 1 week. Illness phase not stated but admitted for study	24-h urinary free cortisol	Cortisol levels SCH 60.1 (SD 58.7) CON 40.5 (SD 27.0)
Breier et al. (1993)	18	11/18 drug free (8–279 days). Stable outpatients with chronic course of illness. BPRS 28	Single plasma cortisol 08.00–09.00	–
Krystal et al. (1993)	12	Drug free for 2 weeks. Hospitalized, acute exacerbation, chronic SCH	Plasma cortisol time not stated	–
Rao et al. (1995)	116	SCH inpatients majority acutely psychotic. 21 were drug naive, 68 drug free for $\geq$3 days, 25 FGA. Study began after at least 3 days in hospital	Plasma cortisol 13.00, 16.00, 19.00, 23.00, 03.00, 07.00, 10.00, 13.00	Daily mean derived from cosinor analysis μmol/L
Wik (1995)	16	Drug free for 3 weeks. Newly admitted, then treated with FGA	Plasma cortisol 08.00 before and after FGA treatment	Before treatment SCH = CON After treatment SCH < CON ($p < 0.001$)
Wilke et al. (1996)	20	Antipsychotic treated. Mean PANSS 59.0	Serum cortisol	–
Kudoh et al. (1997)	22	All receiving FGA, chronic but stable	Plasma cortisol timed in relation to anaesthesia for elective surgery	–
Maguire et al. (1997)	7	Stable residual schizophrenia on depot antipsychotics	Single plasma cortisol 09.00–10.00	–
Elman et al. (1998)	13	FGA. Stable chronic outpatients admitted for study	Plasma cortisol (morning)	–
Jansen et al. (1998)	10	All patients receiving antipsychotics mostly SGA. 5 inpatients, 5 outpatients	Salivary cortisol between 10.00–16.00	–
Jiang and Wang (1998)	21	Inpatients, all receiving FGA. BPRS 48.3	24-h plasma cortisol	$p < 0.01$ (02.00 and 03.00) AUC cortisol SCH = CON
Kudoh et al. (1999)	25	All patients receiving antipsychotics. Chronic SCH	Plasma cortisol 08.30	–
Duval et al. (2000)	41	Drug free for 2 weeks. Inpatients. BPRS 59.4	Plasma cortisol 08.00	–
Jansen et al. (2000)	18	17 receiving SGA and 1 FGA. Outpatients, PANSS 68.39	Salivary cortisol 08.00–20.00 every 2 hours	No significant differences at 08.00 or across whole day
Hundt et al. (2001)	7	Drug free for 7 days. Inpatients with negative and without psychotic symptoms. BPRS 14.6, SANS 14.4	Plasma cortisol 09.00–11.00 (every 30 min)	–
Lee et al. (2001)	5	Drug free for 7 days. Admitted with chronic SCH. BPRS 41	Plasma cortisol 21.00	–
Kaneda et al. (2002)	53	Chronically medicated inpatients. Anxiety similar to controls	Plasma cortisol 06.00–07.00	
Kudoh et al. (2002)	50	FGA treated, stable chronic SCH	Plasma cortisol timed in relation to anaesthesia for orthopaedic surgery	–
Shirayama et al. (2002)	28	Neuroleptics. In and outpatients with an absence of positive sx. Patients split into low ($n = 14$) and moderate negative sx groups ($n = 14$)	Plasma cortisol between 08.30–11.30	$p < 0.01$ (SCH moderate negative sx) SCH low negative sx = CON
Yazici et al. (2002)	58	Drug free for 1 week. Recently admitted. Mean BPRS ~25, SAPS ~30, SANS ~60	Plasma cortisol 09.00	–
Duval et al. (2003)	20	9 drug naive, 11 drug free for 2 years. Acutely psychotic inpatients	Plasma cortisol 09.00 on 2 days	Not significantly different on either day tested

(continued)

Table 2. Continued

Study	SCH (*n*)	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	Comments
Goyal et al. (2004)	10	Most patients taking antipsychotics, 5 prominent positive, low negative sx, 5 prominent negative, low positive sx	Plasma cortisol 08.00	No significant difference between positive and negative
Ritsner et al. (2004)	40	15 received SGA, 15 FGA and 10 both SGA and FGA. Admitted patients but stable. Mean PANSS 68.4	Plasma cortisol 08.00–09.00	–
Strous et al. (2004)	37	Drug free, first episode acutely psychotic inpatients. PANSS 75.2	Plasma cortisol 08.00–10.00	
Brunelin et al. (2008)	15	Remitted outpatients receiving SGA. Admitted for study	Plasma cortisol 09.00	–
Brenner et al. (2009)	30	All patients taking antipsychotics. Stable outpatients	Salivary cortisol 14.00	–

CSF = cerebrospinal fluid, SD = standard deviation. For other abbreviations, see Table 1.

Table 3. Studies finding basal cortisol significantly lower in schizophrenia patients than controls

Study	SCH	Medication, illness phase, symptoms if stated	Cortisol measure and time if stated	p value and comments
Gattaz et al. (1985)	13	Drug free 3–4 weeks. Admitted	CSF cortisol 09.00–10.00	$p < 0.05$
Monteleone et al. (1994)	18	1/18 drug free, rest treated with FGA. Chronic SCH inpatients. SAPS ~ 40, SANS ~37	Plasma cortisol 08.00 measured in November, February and May	SCH < CON at all 3 measurements ($p < 0.001$)
Wik (1995)	16	Drug free for 3 weeks. Newly admitted, then treated with FGA	Plasma cortisol 08.00 before and after FGA treatment	Before treatment SCH = CON After treatment SCH < CON ($p < 0.001$)
Taherianfard and Shariaty (2004)	49	Drug free on first admission. Illness severity not stated	Plasma cortisol 08.00 pre treatment, after 3 weeks' treatment with FGA and at recovery	SCH < CON at all 3 phases of illness ($p = 0.0073$)

For abbreviations, see Table 1.

stable schizophrenia patients than in controls ($p = 0.003$). The studies by Davila et al. (1989), Jansen et al. (1998, 2000), Hundt et al. (2001) Rao et al. (1995), Risch et al. (1992), and Stokes et al. (1984), all found no evidence of differences in cortisol between patients and controls at any of the time points measured.

Risch et al. (1992) reported no statistically significant difference in 24-h, urinary free cortisol between patients and controls but this was probably due to the large variance in cortisol levels: the mean 24-h urinary free cortisol values in the schizophrenia ($n = 32$) and control groups ($n = 73$) were 60.1 (standard deviation (SD) 58.7) and 40.5 (SD 27.0) μg/dL, respectively. In the largest study reported (Rao et al. 1995), 116 drug-free (for at least 3 days), drug-naive and antipsychotic-treated patients were hospitalized for crisis intervention or psychosis before blood cortisol was measured over 24 h. No significant differences in cortisol secretion over the 24-h period were found versus controls, suggesting cortisol secretion was normal in this group. In studies by Jansen et al. (1998, 2000), most schizophrenia patients were taking second-generation antipsychotics, which were likely to have had an effect on cortisol level.

Basal cortisol in drug-naive patients

Antipsychotic medications may influence cortisol levels. Evidence in healthy subjects suggests this effect is minimal with first-generation drugs but significant with second-generation antipsychotics (Cohrs et al., 2006). To examine basal cortisol in patients without the influence of antipsychotic medication, first-episode, drug-naive schizophrenia patients were analysed as a group. Eleven studies measured basal cortisol in such patients (Abel et al., 1996; Kale et al., 2010; Ryan et al., 2003, 2004a, 2004b; Spelman et al., 2007; Strous et al., 2004; Taherianfard and Shariaty, 2004; Venkatasubramanian et al., 2007, 2010; Walsh et al., 2005). In one of these studies (Taherianfard and Shariaty, 2004), basal cortisol was significantly lower in schizophrenia patients than in controls. Basal cortisol levels were similar in schizophrenia patients and controls in the study by Strous et al. (2004). In the other nine studies, basal cortisol was significantly elevated compared with controls. Collectively, these nine studies included 226 of the 312 (72.4%) first-episode drug-naive patients studied, indicating that elevated cortisol secretion is a common finding in these patients.

CRH test

Only one published study, including nine schizophrenia patients and 27 controls, utilized the CRH test (Roy et al., 1986) (Table 4). Six of the patients had been taking fluphenazine for at least 6 months on entry into the study and were studied whilst on medication and then at least 2 weeks after discontinuation of medication. Three patients were studied medication free at study entry, and two of these were also evaluated after at least 2 weeks of fluphenazine treatment. Whilst patients were drug free, ACTH and cortisol response to CRH infusion was similar to that in controls. Treatment with fluphenazine had no effect on response to CRH.

Dexamethasone/CRH test

Just two studies employing the DEX/CRH test in schizophrenia were identified. One of these (Heuser et al., 1994) was excluded as data for the 24 schizophrenia patients were combined with those from patients with other diagnoses. Details of the only other study identified (Lammers et al., 1995) of 24 schizophrenia patients and 24 controls are provided in Table 4. Basal cortisol was statistically significantly greater in patients than in controls ($p < 0.01$) and basal ACTH trended towards being higher in patients ($p < 0.08$). Peak cortisol following DEX and CRH ($p < 0.02$) and cortisol AUC 14:00–18:00 following DEX and CRH was significantly greater in schizophrenia patients than controls ($p < 0.04$). There was no evidence for a difference in ACTH AUC following CRH infusion between patients and controls.

Effects of psychological stress on the HPA axis in schizophrenia

Six studies meeting the inclusion criteria for measuring the effects of psychological stress on HPA function were identified. These included 89 patients with schizophrenia and 144 controls (Table 5). The study by Albus et al. (1982) used a combination of psychological and physical stressors, while

Table 4. Studies using the CRH and DEX CRH test in schizophrenia subjects

Study and test	Population characteristics	Medication and illness phase	Test details	Results
Roy et al. (1986) CRH test	9 admitted SCH patients. 4 male, 5 female Mean age 30.0 (range 22–53) 27 CON	All acutely psychotic, 3 patients were medication free at admission and 6 patients were medicated. Of the 8 medicated patients, only 1 was in remission	All 9 patients were studied medication free ($\geq$2weeks) and 8 whilst on neuroleptics. 1 μg/kg CRH intravenously administered at 20.00. Blood sampled for ACTH and cortisol at regular intervals over 180 min	Basal cortisol SCH = CON (4/9 unmedicated patients had basal cortisol 2 SD above the controls mean) Basal ACTH SCH = CON **CRH while drug free** In the overall SCH group, ACTH and cortisol response to CRH was normal 2 patients with high basal cortisol had an ACTH response well below the mean for the group although within the normal range Trend towards a significant negative correlation between psychosis rating and ACTH response ($r = -0.42$, $p < 0.1$) **CRH while medicated** Treatment with fluphenazine had no effect on basal ACTH or cortisol. Response of ACTH and cortisol following CRH was not significantly different to controls
Lammers et al. (1995) DEX/CRH test	24 SCH patients 6 males, 8 females mean age 34 (SD 9) 24 CON	9 patients were drug free for 3 months; the rest were treated with clozapine ($n = 8$) sulpride ($n = 1$) and typical neuroleptics ($n = 6$) Mean BPRS 41 (15)	Patients given 1.5 mg DEX at 23.00. Following day at 15.00 100 μg CRH was infused. Blood was sampled at regularly from 14.00 to 18.00 for measurement of ACTH and cortisol DST NS prior to CRH measured at 14.00–15.00 (cort > 110 nmol/L)	Basal cortisol SCH > CON ($p < 0.01$) Basal ACTH SCH tended > CON ($p < 0.08$) DST NS prior to CRH 3/24 (13%) SCH, 0 CON DST NS following CRH SCH 6, CON 5 Total DST NS SCH 9/24 (38%) CON 5/24 (21%) AUC cortisol following CRH SCH > CON ($p < 0.04$) Peak cortisol following CRH SCH > CON ($p < 0.02$) ACTH following CRH SCH = CON For SCH, AUC cortisol post-CRH was significantly greater in unmedicated than medicated patients ($p < 0.05$)

ACTH, adrenocorticotropin hormone, CRH, corticotropin releasing hormone, DEX, dexamethasone, DST NS, non suppression of cortisol following DEX. For other abbreviations, see Tables 1 and 2.

that by Goldman et al. (2007) used the cold pressor test (immersion of a limb in iced water), which is reported to invoke an HPA response via both psychological and physical components (Bullinger et al., 1984). The study reported by Breier et al. (1988a) measured response to the psychological stress associated with lumbar puncture. The remaining studies (Brenner et al., 2009; Jansen et al., 1998, 2000) all used a public speaking task as the psychological stressor. The results from five of these studies (Albus et al., 1982; Breier et al., 1988a; Goldman et al., 2007; Jansen et al., 1998, 2000) were consistent, indicating that people with schizophrenia have a blunted cortisol response to psychological stress compared with controls. In the remaining study (Brenner et al., 2009), there was a trend towards a lower cortisol response to psychological stress in schizophrenia patients. Two of the studies (Breier et al., 1988a; Goldman et al., 2007) also measured ACTH and both found that this too had a blunted response to stress.

The dexamethasone suppression test in schizophrenia

The search identified 85 studies including 2722 schizophrenia patients that met the inclusion criteria, as presented in Table 6. Non-suppression of cortisol following DEX ranged from 0–81%. From the total group of schizophrenia patients studied, 731/2722 (26.9%) were classified as non-suppressors. Since antipsychotic medication may affect DST results (Tandon et al., 1991), medicated and drug-free patients were analysed separately. For non-medicated schizophrenia patients (no neuroleptic medication for $\geq$2 weeks prior to the DST), 227/773 (29.4%) were classified as non-suppressors. Of the 1949 medicated schizophrenia patients, 504 (25.9%) were classified as non-suppressors, suggesting that antipsychotic medications themselves had little effect on DST results.

Several studies correlated symptoms such as depressive, negative and positive symptoms with DST outcomes, as

Table 5. Studies measuring HPA axis response to psychosocial stress in schizophrenia patients

Study	Population characteristics	Test details and outcome HPA measures	Results
Albus et al. (1982)	12 acutely psychotic, SCH patients, drug free for 4 weeks 27 CON	Cold pressor test, noise, mental arithmetic, active relaxation Cortisol response	Schizophrenia patients had significantly higher cortisol levels than controls at rest and during the tests ($p < 0.05$) Schizophrenia patients had a diminished cortisol response to stress compared with controls
Breier (1988a)	10 drug free (>3 weeks), chronic SCH patients 8 CON	Stress associated with lumbar puncture at 08.00–09.00 Plasma cortisol and ACTH	Basal cortisol SCH = CON SCH patients had no significant elevations in plasma cortisol or ACTH during lumbar puncture CON subjects had significant increase in ACTH ($p < 0.05$) and cortisol ($p < 0.05$) 15-min cortisol change SCH < CON ($p < 0.05$) Level of psychosis in SCH patients was negatively correlated with ACTH level, i.e. higher stress-related ACTH levels were associated with lower level of psychosis
Jansen et al. (1998)	10 SCH in and outpatients receiving antipsychotics 10 CON	Public speaking task Salivary cortisol	Basal cortisol SCH = CON SCH patients had a significantly smaller salivary cortisol response to stress than CON ($p = 0.033$)
Jansen et al. (2000)	18 medicated SCH outpatients 21 CON	Public speaking task and exercise (10 min bike home trainer) Salivary cortisol	Basal and cortisol day profile SCH = CON Salivary cortisol response to public speaking SCH < CON ($p < 0.01$) Salivary cortisol response to exercise SCH = CON
Goldman et al. (2007)	9 medicated SCH (2/9 schizoaffective), in and outpatients admitted at least 3 weeks before the study and optimized on FGA (8/9) and SGA (1/9) medication PANSS total 57.2 12 CON	Cold pressor test performed in the evening	ACTH ($p = 0.021$) and cortisol response ($p = 0.001$) to cold pressor test was blunted in SCH patients relative to controls
Brenner et al. (2009)	30 chronic but stable SCH patients. 29 CON	Modified version of Trier social Stress Test (TSST) Salivary cortisol	Basal cortisol SCH = CON Cortisol increased significantly during the test for CON ($p = 0.002$) but not for SCH ($p = 0.369$) Acute cortisol response to stress SCH trend < CON ($p = 0.062$). When body mass index (BMI) and psychosis were controlled for cortisol response to stress, SCH < CON ($p < 0.05$) AUC cortisol showed a trend for SCH to secrete less cortisol than CON ($p = 0.062$)

For abbreviations, see Tables 1 and 4.

Table 6. Dexamethasone Suppression Test in schizophrenia

Study	Study setting and patient symptoms (as described)	Non-suppression medicated patients	Non-suppression drug-free patients	Associations with symptoms where tested
Schlesser et al. (1980)	Mostly inpatients	0/48 (0%)	–	–
Dewan et al. (1982)	Chronic SCH	6/20 (30%)	–	No association of post-DEX cortisol with HAM-D or BPRS
Rothschild et al. (1982)	Psychotic inpatients	2/14 (14%)	–	–
Castro et al. (1983)	Chronic SCH	7/23 (30%)	–	–
Coppen et al. (1983)	Chronic SCH inpatients	10/46 (22%)	–	NS associated with negative not positive symptoms
Targum (1983)	Hospitalized SCH patients	1/14 (7%)		–
Banki et al. (1984)	Hospitalized, acutely psychotic	13/34 (38%)	–	Paranoid SCH < catatonic and hebephrenic
Berger et al. (1984)	Admitted SCH patients	7/23(30%) on admission 4/21 (19%) 7–10 days later	–	–
Hwang et al. (1984)	SCH inpatients	2/13 (15%)	–	–
Meltzer et al. (1984)	No details	7/36 (19%)	–	–
Munro et al. (1984)	Residual SCH outpatients	7/46 (15%)	–	NS associated with depressive symptoms
Nelson et al. (1984)	Admitted SCH patients	4/14 (29%)	–	–
Rihmer et al. (1984)	Paranoid SCH	1/20 (5%)	–	–
Sauer et al. (1984)	Admitted SCH patients	5/20 (25%)	–	–
Sawyer and Jeffries (1984)	20 SCH inpatients	7/20 (35%)	–	NS associated with melancholic depression not depressed mood
Stokes et al. (1984)	Hospitalized chronic SCH	2/12 (17%)		–
Banki et al. (1985)	Recently hospitalized SCH	–	10/20 (50%)	–
Baumgartner et al. (1985)	Recently hospitalized SCH	11/22 (50%)	–	–
Dam et al. (1985)	SCH inpatients	5/15 (33%)	–	–
Harris (1985)	Chronic long stay SCH	–	4/12 (33%)	No association of negative symptoms with NS
Herz et al. (1985)	Recently admitted SCH acutely psychotic	9/13 (69%) 1/5 (20%) of the non-suppressors after 7 days' antipsychotic therapy	–	–
Morphy et al. (1985)	Admitted SCH patients	6/13 (46%)		
Saffer et al. (1985)	Chronic long stay SCH	10/50 (20%)	–	NS associated with negative symptoms
Asnis et al. (1986)	Chronic and subchronic SCH inpatients	4/17 (24%)	–	–
Banki et al. (1986)	Recently hospitalized SCH	–	7/20 (35%)	–
Cook et al. (1986)	Acutely admitted SCH	5/25 (20%)	–	–
Doran et al. (1986)	SCH inpatients	–	2/13 (15%)	No association of NS with depression
Hubain et al. (1986)	Acute, recently admitted SCH	10/22 (45%)	–	–
McMahon et al. (1986)	Recently admitted, acutely psychotic chronic SCH	1/12 (8%)	–	–
Moller et al. (1986)	Acutely psychotic SCH	12/20 (60%) day 1 7/19 (37%) day 7 6/12 (46%) day 23	–	No association with depressive symptoms. Negative correlation of NS with severity of SCH symptoms
Pickar et al. (1986)	Chronic recently admitted SCH	–	5/24 (21%)	–
Sora et al. (1986)	Recently admitted SCH	7/28 (25%)	–	–
Tsoi et al. (1986)	Chronic SCH	7/61 (11%)	–	NS not associated with depression, positive or negative
Wik et al. (1986)	Acutely admitted SCH	4/15 (27%)	17/21 (81%)	–
Banki et al. (1987)	Recently hospitalized SCH	–	6/23 (26%)	–
Holsboer-Trachsler et al. (1987)	Severe, acute, admitted SCH	15/31 (48%) 1st test 4–5 days	–	–

(continued)

Table 6. Continued

Study	Study setting and patient symptoms (as described)	Non-suppression medicated patients	Non-suppression drug-free patients	Associations with symptoms where tested
		4/31 (13%) 2nd test 4 weeks		
Hwu et al. (1987)	SCH inpatients	11/60 (18%)	–	NS associated with depression
Joseph et al. (1987)	Non-depressed acute, chronic and subchronic SCH	0/37 (0%) 2 patients NS but compliance with DEX unclear	–	–
Joyce et al. (1987)	Recently admitted SCH	2/10 (20%)	–	–
Krishnan et al. (1987)	Recently admitted SCH	2/15 (13%)	–	–
Pandey et al. (1987)	Admitted to research unit	–	4/22 (18%)	–
Perenyi et al. (1987)	Recently admitted SCH	6/30 (20%)	–	No association with anxiety/ depression
Zhou et al. (1987)	Hospitalized SCH	6/48 (13%)	–	–
Aleem et al. (1988)	SCH inpatients	6/19 (32%)	–	No association with depression or negative symptoms
Coryell et al. (1988)	Admitted SCH	2/13 (15%)	–	–
Keshavan et al. (1988)	Chronic SCH	4/16 (25%)	–	Post-DEX cortisol positively correlated with depression and duration of illness. No association with psychosis
Kiriike et al. (1988)	Outpatient and hospitalized SCH	2/22 (9%)	–	–
Lu et al. (1988)	SCH inpatients	–	13/36 (36%)	No association of pre or post-DEX cortisol with depression
Sharma et al. (1988)	SCH inpatients		8/44 (18%)	No association with depression
Whiteford et al. (1988)	Chronic SCH outpatients with prominent negative symptoms	9/40 (23%)	–	No association with depression or negative symptoms
Altamura et al. (1989)	SCH inpatients	22/54 (40%)	–	NS associated with negative symptoms
Coryell and Zimmerman (1989)	Recently admitted SCH	8/31 (26%)	–	–
Horodnicki et al. (1989)	Paranoid SCH	9/20 (45%) prior to treatment 4/20 (20%) after 4 weeks' treatment	–	–
Keshavan et al. (1989)	Recently admitted SCH	–	3/27 (11%)	No association with negative or depressive symptoms. Trend to association with positive symptoms and BPRS total score
McGauley et al. (1989)	Long stay, chronic SCH inpatients	4/28 (14%)		Post-DEX cortisol associated with negative symptoms
Tandon et al. (1989)	Recently admitted SCH	0/20 (0%) after 4 weeks' treatment	7/20 (35%)	Initial NS associated with negative symptoms NS associated with good outcome at 4 weeks
Wolkowitz et al. (1989)	SCH patients	–	4/16 (25%)	
Addington and Addington (1990)	Voluntary admitted SCH	6/50 (12%)	–	NS associated with depression
Harris et al. (1990)	Recently admitted SCH	5/35 (14%)	–	–
Hwu and Lin (1990)	Recently admitted SCH	18/49 (37%) 1st week admission 6/38 (16%) 3rd week admission 4/26 (15%) 1 week before discharge 3/32 (9%) 1-year follow-up	–	–
Minas et al. (1990)	Recently admitted SCH	3/20 (15%)		

(continued)

Table 6. Continued

Study	Study setting and patient symptoms (as described)	Non-suppression medicated patients	Non-suppression drug-free patients	Associations with symptoms where tested
				NS not associated with depression, negative or positive symptoms
Monteleone et al. (1990)	Chronic SCH inpatients	9/32 (28%)	–	–
Steiner et al. (1990)	Newly admitted SCH	0/12 (0%)	–	–
Wahby et al. (1990)	Recently admitted SCH	–	1/10 (10%)	–
Newcomer et al. (1991)	SCH inpatients	–	3/21 (14%)	Post-DEX cortisol associated with negative symptoms and cognitive deficits but not depression. Post-DEX cortisol negatively associated with positive symptoms
Tandon et al. (1991)	Recently admitted SCH	6/44 (14%) after 4 weeks' treatment	22/58 (38%) at baseline	Post-DEX cortisol correlated with negative symptoms but not global severity, positive or depressive symptoms at baseline. No associations at 4 weeks
Coryell and Tsuang (1992)	Admitted SCH	5/20 (25%)	–	–
Pandey et al. (1992)	SCH inpatients	11/34 (32%)	–	–
Rybakowski and Plocka (1992)	SCH inpatients	36/105 (34%)		–
Garyfallos et al. (1993)	Chronic SCH inpatients	4/30 (13%)	–	No significant correlations of post-DEX cortisol with BPRS, depression or negative symptoms
Goldman et al. (1993)	SCH inpatients (25% polydipsic)	7/53 (13%)	12/53 (27%)	NS was more common in polydipsic patients during treatment with antipsychotics (38% vs. 5%)
Jones et al. (1994)	Hospitalized SCH	–	12/57 (21%)	Post-DEX cortisol correlated with suicide attempt, depression, negative and positive symptoms (BPRS +ve scale 1)
Mauri et al. (1994)	Acutely psychotic SCH inpatients	6/24 (25%)	–	No association of NS with BPRS total
Monteleone et al. (1994)	SCH inpatients	0/18 (0%) (November DST)	–	DST repeated in Feb 4/18 (22% NS) and May 0/18 (0%)
Goldman et al. (1996)	Admitted SCH	–	18/49 (37%)	No association of post-DEX cortisol with family history of depression
Lewis et al. (1996)	Admitted SCH	–	38/96 (40%)	No association with suicide attempt
Tandon et al. (1996)	SCH inpatients	–	14/35 (40%)	Post-DEX cortisol associated with negative symptoms but not depressive or positive symptoms
Pivac et al. (1997)	Admitted SCH	44/80 (55%)	–	NS similar in positive and negative symptoms
Ismail et al. (1998)	Paranoid SCH in and outpatients	1/60 (2%)	–	Post-DEX cortisol correlated with depression and BPRS but not negative symptoms
Jiang and Wang (1998)	Paranoid SCH inpatients	0/21 (0%)	–	–
Muck-Seler et al. (1999)	Admitted SCH	43/86 (50%)	–	–
Duval et al. (2000)	Paranoid SCH inpatients	–	7/41 (17%)	–
Plocka-Lewandowska et al. (2001)	Hospitalized acute SCH	13/32 (41%) 8/32 (25%) 9 years later	–	NS associated with suicide attempt
Yazici et al. (2002)	Admitted SCH	24/58 (41%)	–	NS associated with good 1 year outcome
Ceskova et al. (2006)	First episode hospitalized SCH	3/56 (5%) after acute treatment 9/56 (16%) after 1 year	10/56 (18%)	Trend for NS to be associated with good outcome. Post-DEX cortisol correlated with negative symptoms following acute treatment

HAM-D, Hamilton depression rating scale, NS, non suppressor of cortisol following DEX. For other abbreviations, see Tables 1 and 4.

detailed in Table 6; however, no clear picture of correlation emerged. Of the 19 studies that looked for a correlation between negative symptoms and non-suppression of post DEX cortisol levels, 10 found a correlation (Altamura et al., 1989; Ceskova et al., 2006; Coppen et al., 1983; Jones et al., 1994; McGauley et al., 1989; Newcomer et al., 1991; Saffer et al., 1985; Tandon et al., 1989, 1991, 1996), and nine did not (Aleem et al., 1988; Garyfallos et al., 1993; Harris, 1985; Ismail et al., 1998; Keshavan et al., 1989; Minas et al., 1990; Pivac et al., 1997; Tsoi et al., 1986; Whiteford et al., 1988).

Seven studies found a correlation of non-suppression with depression (Addington and Addington, 1990; Hwu et al., 1987; Ismail et al., 1998; Jones et al., 1994; Keshavan et al., 1988; Munro et al., 1984; Sawyer and Jeffries, 1984) while 15 did not (Aleem et al., 1988; Dewan et al., 1982; Doran et al., 1986; Garyfallos et al., 1993; Keshavan et al., 1989; Lu et al., 1988; Minas et al., 1990; Moller et al., 1986; Newcomer et al., 1991; Perenyi et al., 1987; Sharma et al., 1988; Tandon et al., 1991, 1996; Tsoi et al., 1986; Whiteford et al., 1988). Goldman et al. (1996) found no association of non-suppression with a family history of depression.

Seven studies found no correlation between positive symptoms and non-suppression of cortisol (Coppen et al., 1983; Keshavan et al., 1988; Minas et al., 1990; Pivac et al., 1997; Tandon et al., 1991, 1996; Tsoi et al., 1986), with one study finding a positive association (Jones et al., 1994), one a trend towards a positive correlation (Keshavan et al., 1989) and one finding a negative association (Newcomer et al., 1991). Two studies found an association of post-DEX cortisol with suicide attempt (Jones et al., 1994; Plocka-Lewandowska et al., 2001), while a study by Lewis et al. (1996) found no such association.

The studies reported by Berger et al. (1984), Herz et al. (1985), Holsboer-Trachsler et al. (1987), Horodnicki et al. (1989), Hwu and Lin (1990), Moller et al. (1986), Tandon et al. (1989, 1991), and Wik et al. (1986), all included a DST performed on newly admitted psychotic patients and then repeated following varying lengths of antipsychotic treatment. These studies all demonstrated high non-suppression rates on admission (range 30–81%), and in each case there was a large reduction in the percentage of non-suppressors following antipsychotic treatment (range 0–46%), during which time there was an assumed clinical improvement. In the longest study over time, Plocka-Lewandowska et al. (2001) found non-suppression in 41% of the acutely hospitalized sample; 25% were non-suppressors 9 years later.

Basal measures of CRH and ACT

In total, 21 studies measured basal CRH and/or ACTH in 539 schizophrenia patients (Table 7). Basal CRH in CSF was measured in five of these studies (Banki et al., 1987, 1992; Nemeroff et al., 1984; Nishino et al., 1998; Risch et al., 1992). Four of these found basal CRH to be similar in schizophrenia and controls, and in only one of these studies (Banki et al. 1987) was there any evidence for increased basal CRH in schizophrenia. However, in this study, 6/23 (26%) schizophrenia patients had a CRH value higher than the greatest value in any control subject. Thus, the mean CRH for schizophrenia patients was statistically significantly higher than that for control subjects ($p < 0.001$), but the authors suggested that the mean value was skewed by the data from the three schizophrenia patients with extremely high CRH values.

Seventeen of the studies measured basal ACTH. The studies reported by Duval et al. (2000, 2003), Elman et al. (1998), Hundt et al. (2001), Risch et al. (1992), Roy et al. (1986), van Cauter et al. (1991) (which measured 24-h ACTH), and Yazici et al. (2002) all found no difference between basal ACTH in schizophrenia patients and controls. These studies also all reported no difference in cortisol in these patients indicating a normal effect of ACTH on cortisol secretion. In addition:

Kathol et al. (1992) found a trend towards lower basal ACTH in schizophrenia patients than controls ($p = 0.07$) but similar cortisol levels in patients and controls

Kudoh et al. (1997) reported significantly lower basal ACTH ($p < 0.05$) but similar cortisol in schizophrenia patients and controls

Brambilla et al. (1984) found non-significantly higher basal cortisol levels in schizophrenia patients compared with controls: 14/37 (38%) schizophrenia patients had an ACTH level above the range of the controls

Lammers et al. (1995) reported basal ACTH tended to be higher in schizophrenia patients ($p < 0.08$), resulting in a significantly higher basal cortisol level ($p < 0.01$)

Kaneda et al. (2002) and Brunelin et al. (2008) found significantly elevated ACTH in patients compared with controls ($p < 0.0015$ and $p < 0.04$, respectively), but similar basal cortisol levels in patients and controls

Ryan et al. (2004a) and Walsh et al. (2005) found evidence of increased basal ACTH and cortisol in first-episode, drug-naive schizophrenia patients versus controls

Shirayama et al. (2002) only found evidence of increased basal ACTH in patients with moderate negative symptoms ($p < 0.05$), in contrast to those with low negative symptoms where ACTH did not differ between patients and controls.

Discussion

The aim of this systematic review was to firstly examine HPA axis function in people with schizophrenia, and then to assess if any evidenced dysfunction could be contributing to the poor physical health and premature mortality seen in patients with schizophrenia. The two most commonly studied areas of HPA axis function, i.e. the direct measurement of basal cortisol and the DST, provided highly heterogeneous results, making interpretation complex and firm conclusions on the state of HPA axis function in schizophrenia difficult. Other areas examined, such as the HPA axis response to psychological stressors, provided more consistent findings, but results are still open to interpretation. Despite these complexities, this review has identified a number of significant differences between schizophrenia patients and controls, indicating there may be clinically relevant HPA axis dysfunction in patients with schizophrenia. These findings are discussed below along with possible confounders. Finally, the role of these changes

Table 7 Studies measuring basal CRH and ACTH

Study	Subjects	Illness phase and setting and medication use	Measurement details	Findings
Brambilla et al. (1984)	37 SCH 21 CON	Drug free ≥10 days. All had severe thought disorder and delusions	Plasma ACTH 09.00	Basal ACTH SCH = CON although 14 SCH patients had basal ACTH above the CON range
Nemeroff et al. (1984)	11 SCH 10 CON	Drug free for ≥2 weeks, setting and illness phase not stated.	CSF CRH 09.00	CSF CRH SCH = CON
Roy et al. (1986)	9 SCH 27 CON	Recently hospitalized, acutely psychotic. Drug free for ≥2 weeks	Plasma ACTH and cortisol	Basal ACTH and cortisol SCH = CON
Banki et al. (1987)	23 SCH 138 neurological CON	Recently hospitalized, severely ill, drug free for ≥2 weeks	CSF CRH 09.00–10.00 (4–7 days after admission)	CSF CRH SCH > CON ($p < 0.001$) 6/23 (26%) of SCH subjects had CRH higher than the highest CON value
van Cauter et al. (1991)	9 SCH 9 CON	Drug free for 3 weeks. Neuroleptic free for 9 weeks. Recently hospitalized for exacerbation of chronic illness	24-h plasma corticotropin (ACTH) and cortisol measured at 15-min intervals	Circadian rhythm of cortisol secretion was normal in SCH ACTH SCH = CON at all times over 24-h period 24-h cortisol SCH = CON Cortisol SCH > CON from 00.00 to 04.00 hours ($p < 0.01$)
Banki et al. (1992)	91 SCH 29 neurological CON	Recently hospitalized, actively psychotic, drug free for ≥2 weeks	CSF CRH 09.00–10.00 (3–6 days after admission)	CSF CRH SCH = neurological CON
Kathol et al. (1992)	5 SCH 13 CON	SCH inpatients drug free for ≥2 weeks	Plasma ACTH and cortisol (at 16.00)	Basal ACTH trended to SCH < CON ($p = 0.07$) Basal cortisol SCH = CON
Risch et al. (1992)	45 SCH 94 CON	Drug free for 1 week. No indication of illness phase but admitted for study	CSF CRH and ACTH (obtained 07.00–09.00) 24-h UFC	UFC SCH = CON CSF CRH and ACTH SCH = CON
Lammers et al. (1995)	24 SCH 24 CON	9 patients drug free for 3 months, the rest treated with clozapine and typical neuroleptics	Plasma ACTH and cortisol	Basal ACTH tended SCH > CON ($p < 0.08$) Basal cortisol SCH > CON ($p < 0.01$)
Kudoh et al. (1997)	22 SCH 20 CON	All receiving FGA, chronic but stable	Plasma ACTH and cortisol	Basal ACTH SCH < CON $p < 0.05$) Basal cortisol SCH = CON
Elman et al. (1998)	13 SCH 11 CON	Out patients all receiving FGA	Plasma ACTH and cortisol	Basal ACTH and cortisol SCH = CON
Nishino et al. (1998)	12 SCH 14 CON	Drug free for ≥2 weeks Hospitalized inpatients	CSF CRH obtained 07.00–08.00	CSF CRF SCH = CON
Duval et al. (2000)	41 SCH 27 CON	Hospitalized SCH drug free for ≥2 weeks	Plasma ACTH and cortisol (08.00)	Basal ACTH and cortisol SCH = CON
Hundt et al. (2001)	7 SCH 10 CON	Inpatients with negative and without psychotic symptoms. Drug free for ≥7 days	Plasma ACTH and cortisol (every 30 min from 09.00–11.00)	Basal ACTH SCH = CON Basal cortisol SCH = CON
Kaneda et al. (2002)	53 SCH 23 CON	Chronically medicated inpatients	Plasma ACTH and cortisol (06.00–07.00)	Basal ACTH SCH > CON ($p = 0.0015$) Basal cortisol SCH = CON
Shirayama et al. (2002)	28 SCH 13 CON	In and outpatients with stable sx and an absence of positive sx. Patients split into low ($n = 14$) and moderate negative sx groups ($n = 14$). All patients on neuroleptics	Plasma ACTH and cortisol (single sample between 08.30–11.30)	Basal ACTH SCH with moderate negative sx SCH > CON ($p < 0.05$) Basal ACTH SCH with low negative Sx SCH = CON Basal cortisol SCH with moderate negative sx > CON ($p < 0.01$) Basal cortisol SCH with low negative sx SCH = CON
Yazici et al. (2002)	58 SCH 30 CON	Admitted SCH patients. Drug free for ≥1 week	Plasma ACTH obtained at 08.00, cortisol at 09.00)	Basal ACTH and cortisol SCH = CON
Duval et al. (2003)	20 SCH 23 CON	SCH inpatients. 11 drug naïve, 9 drug free for >2 years	Plasma ACTH and cortisol (07.00–09.00)	Basal ACTH and cortisol SCH = CON

(continued)

Table 7 Continued

Study	Subjects	Illness phase and setting and medication use	Measurement details	Findings
Ryan et al. (2004b)	12 SCH 12 CON	Hospitalized first episode drug naive	Plasma ACTH, AVP and cortisol (at 20-min intervals 13.00–16.00)	Basal cortisol and AVP SCH = CON Basal ACTH SCH > CON ($p < 0.05$) AUC ACTH SCH > CON ($p < 0.02$) AUC cortisol SCH > CON ($p < 0.01$) AUC AVP SCH < CON ($p < 0.02$)
Walsh et al. (2005)	10 SCH 10 CON	Hospitalized, first episode, drug naive	Plasma ACTH and cortisol (at 13.00)	Basal ACTH SCH > CON ($p < 0.001$) Basal cortisol SCH > CON ($p < 0.02$)
Brunelin et al. (2008)	15 SCH 15 FDR 14 CON	Remitted outpatients admitted for study. All receiving SGA	Plasma ACTH and cortisol	Basal ACTH varied across groups ($p < 0.04$): SCH 19.8 (8.7), FDR 12.6 (5.6), CON 16.6 (7.4) ng/mL Basal cortisol SCH = FDR = CON

AVP, arginine vasopressin, FDR, first-degree relatives, antipsychotic, UFC, urinary free cortisol. For other abbreviations, see Tables 1. 2 and 4.

in HPA axis function is discussed with regard to physical disease and premature mortality in schizophrenia patients.

Basal HPA axis activity

Basal cortisol is assumed to be a measure of the secretion of cortisol in the unstressed or resting state and would give an indication of hyper-, hypo- or normal cortisol secretion under basal conditions. This systematic review found evidence of elevated basal cortisol in some but not all schizophrenia patients compared with controls. However, measurement of basal cortisol is confounded by several factors, which may account for the heterogeneous results described. Most importantly, psychological stress influences cortisol secretion and, for this reason, a fair comparison of basal cortisol secretion between patients and controls would require both groups to be under similar levels of psychological stress. In practical terms this is very difficult to achieve for a number of reasons. Schizophrenia patients are exposed to a broad range of psychological stressors; some true stressors experienced by the population at large, but others which can be termed 'pseudostressors' (Dinan, 2004). These emanate from subjective space and are only experienced by people with schizophrenia and other psychotic illness. They are represented by the core symptoms of schizophrenia such as delusions and hallucinations, and can have profound emotional intensity. They are likely quite different to the stresses experienced by the rest of the population. Given the behavioural disturbance these symptoms can produce, it is reasonable to assume they may influence endocrinological changes in the HPA axis. It is also quite possible that the type of psychotic symptoms, and the perception of these symptoms as stressful or not by the individual, will influence the cortisol level. For example, acute persecutory delusions are more likely to be perceived as stressful by an individual than delusions of grandeur, and therefore may influence cortisol secretion differently. The type of stress and whether it is social-evaluative and uncontrollable has been demonstrated to influence cortisol level in healthy subjects (Dickerson and Kemeny, 2004) and may also be applicable to those with schizophrenia (Jones and Fernyhough, 2007). Many studies of basal cortisol and the DST included symptomatic patients, many of whom were acutely psychotic and were therefore likely to be under different levels and types of stress than the control populations. It is therefore difficult to interpret whether any differences in cortisol level are due to different levels of stress experienced by patients compared with controls, or to a difference in basal function of the HPA axis.

Patients were also frequently hospitalized due to their clinical condition, and this too may be experienced as a stressful event by a patient, thus also invoking an increased stress response. Another confounding factor may be the use of antipsychotic medications. Antipsychotics can influence cortisol levels in several ways. First, by reducing the symptoms of schizophrenia they may reduce the levels of pseudostress associated with psychotic illness and consequently also reduce cortisol levels. Second, antipsychotics may influence the secretion of cortisol as a direct result of their pharmacological actions and mask the HPA axis hyperfunction seen in the untreated state. It has previously been discussed that the reduction of cortisol seen during clozapine treatment could be a non-specific reduction in stress-induced activation of the HPA axis or a direct effect of clozapine on cortisol secretion (Meltzer, 1989). This effect has also been examined in healthy subjects in order to negate the effect of improving symptom expression on cortisol secretion. Evidence suggests that first-generation antipsychotics have little effect on cortisol level in healthy subjects, but that second-generation drugs, notably olanzapine, quetiapine and clozapine, reduce ACTH and cortisol levels, possibly through their serotonergic, adrenergic and histominergic activities (Cohrs et al., 2006).

This systematic review found evidence of elevated basal cortisol in some schizophrenia patients compared with controls, but in terms of whether this actually evidences any dysfunction of the HPA axis or reflects the phase of illness and/or clinical setting, and therefore differences in perceived stress levels between patients and controls, needs careful interpretation in view of the above confounders.

Evidence for elevated cortisol was found most consistently in first-episode, drug-naive schizophrenia patients. Studies in these patients are free from the confounding effects of medication. However, in all of these studies, patients were likely to be experiencing some level of psychological stress either due to their psychotic symptoms and/or admission to a

psychiatric hospital. For this reason it is not possible to conclude that these studies provide evidence of HPA axis dysfunction per se, as the elevated cortisol levels commonly found could be the result of a normal HPA axis response to stress. In one of these studies, symptoms were mild to moderate and hospital admission was voluntary (Ryan et al., 2004b), but it is still not possible to entirely rule out the effects of the stress associated with the patients' clinical condition or setting. In another first-episode study reported by the same group (Ryan et al., 2004a), patients were only mildly ill at entry but were hospitalized with a mean brief psychiatric rating scale (BPRS) score of 32.1 (+/−1.8). At baseline, these patients had significantly higher cortisol than control subjects ($p < 0.003$). Following 6 months of treatment with either olanzapine or risperidone, mean BPRS scores had fallen to 21.6 (+/−0.8) and patients were presumably discharged from hospital. This was accompanied by a significant reduction in cortisol from the pre-treatment mean ($p < 0.05$). Decreased cortisol levels in these patients could be due to successful treatment of schizophrenia symptoms with a resultant reduction of stress, or to the direct effect of antipsychotics on cortisol secretion.

Although the study reported by Strous et al. (2004) found no difference in basal cortisol between first-episode schizophrenia patients and controls, it did demonstrate significant associations of cortisol with negative ($r = 0.35$, $p = 0.036$), general ($r = 0.35$, $p = 0.034$) and total positive and negative syndrome scale (PANSS) scores ($r = 0.33$, $p = 0.045$). In this study, levels of the adrenal steroid dehydroepiandrosterone (DHEA) and its sulphated form DHEA-S were significantly elevated in schizophrenia patients. These steroids have anti-glucocorticoid activity and have been shown to reduce cortisol levels in healthy individuals (Wolf et al., 1997). They could, therefore, explain the non-elevation of cortisol in this group.

Venkatasubramanian et al. (2007, 2010) and Spelman et al. (2007) found elevated cortisol levels in drug-naive patients and, in contrast to Strous et al. (2004), found no direct association of cortisol with psychopathology scores. However, in the Venkatasubramanian et al. (2010) study, treatment with primarily olanzapine and risperidone resulted in both symptom and cortisol reduction and an increase in insulin-like growth factor-1 (IGF-1). Furthermore, the greater the increase in IGF-1, the greater the reduction in positive symptoms ($r = 0.39$, $p = 0.02$). That there was also a significant positive correlation between the magnitude of increase in IGF-1 level and the magnitude of reduction in cortisol level ($r = 0.52$, $p = 0.002$) indicates cortisol may be indirectly associated with positive symptoms possibly via its effects on IGF-1.

The DST is a test of delayed feedback mechanisms in the HPA axis which may then lead to hypersecretion of cortisol. In the only study using the DST in first-episode schizophrenia patients, Ceskova et al. (2006) found an association of anxiety with pre-treatment cortisol levels in mostly drug-naive patients. There was a DST non-suppression rate of 17.9% at medication-free baseline and, following acute treatment, a significant association of post-DEX cortisol with negative symptoms was found. After acute treatment and clinical improvement, the number of non-suppressors to the DST had fallen to 5.3% and was 16.1% after 1 year. This increase in DST non-suppressors after 1 year was partially explained by clinical deterioration and non-compliance in some patients. Collectively, these studies demonstrate that cortisol level may be associated with the symptoms of schizophrenia and may decrease with improving clinical picture.

A possible weakness of this systematic review is that some studies that did not meet the inclusion criteria may still provide useful information of HPA axis function in schizophrenia. Two studies, not included in this review due to the absence of a control group, add strength to the view that cortisol level may be related to symptoms. Sachar et al. (1970) measured glucocorticoid levels across illness phases in first-episode psychosis diagnosable as acute schizophrenic reaction. Four male patients were managed as inpatients by intensive nursing without the use of antipsychotic medication. Twenty-four hour urinary 17-hyydroxycorticosteroid (17-OHCS) and 08 : 00 plasma 17-OHCS were measured several times a week. The period of acute psychotic turmoil was associated with a marked 250% increase from basal levels of corticosteroid in each patient. Corticosteroids fell to normal levels in one patient following development of an organized psychotic system and then rose again as the patient moved into a depressive phase of illness. In the other three patients, corticosteroid levels reduced through a recovery phase and returned to basal levels on total recovery and discharge. These observations provide evidence for a relationship between symptoms, phase of illness and cortisol level in first-episode patients without the complication of medication use. However, for ethical reasons, this study is unlikely to be replicated today. Franzen (1971) reported the association of cortisol with symptoms in 18 female, medicated, chronic schizophrenia patients by measuring 24-h serum cortisol and correlating with symptoms measured by the RP scale, which quantifies mental status in psychotic patients (Rockland and Pollin, 1965). A relationship between mental status and diurnal rhythm of serum cortisol was found such that elevated morning cortisol and a steeper declination of the cortisol diurnal curve correlated with anxiety, thought disorder and delusions and paranoid traits.

Associations of symptoms and cortisol levels have also been explored in chronic rather than acutely ill patients. Christie et al. (1986) found that morning plasma cortisol levels correlated with BPRS score ($p < 0.05$). Patients diagnosed with schizophrenia using RDC had significantly elevated afternoon cortisol compared with controls, but in schizophrenia patients classified according to the criteria of Feighner (Feighner et al., 1972), which yielded a group of less acutely ill patients, there were no differences in cortisol levels, suggesting increased cortisol may be linked to symptoms. Studies have also found an association of cortisol with negative symptoms. Altamura et al. (1989) reported that patients with prominent negative symptoms and low levels of positive symptoms had similar basal cortisol at 08 : 00 but significantly higher basal cortisol at 16 : 00 ($p < 0.01$) than patients with prominent positive symptoms and low levels of negative symptoms. Shirayama et al. (2002) examined schizophrenia patients with an absence of positive symptoms who were clinically stable for 2 months before the study. Patients were grouped into moderate and low negative symptoms, based on the scale for assessment of negative symptoms (SANS). Only those with moderate negative symptoms had significantly elevated cortisol compared with controls.

The study by Zhang et al. (2005) found schizophrenia patients had significantly higher cortisol levels than controls both pre- and post-treatment; cortisol significantly reduced from baseline during treatment with both risperidone and haloperidol, although to a significantly greater degree with risperidone ($p = 0.014$) Cortisol was significantly correlated with negative symptoms at both baseline ($r = 0.28$, $p = 0.02$) and post-treatment ($r = 0.34$, $p = 0.005$) and with PANSS total score post-treatment ($r = 0.30$, $p = 0.01$). The study reported by Breier et al. (1988a) found no association of basal ACTH or other neuroendocrine measures with global psychosis.

As described earlier, studies of the DST in schizophrenia patients have also looked for correlations of symptoms with non-suppression of cortisol which would indicate a faulty feedback mechanism in the HPA axis. The results indicated there is no consistent association of post-DEX cortisol or non-suppression with negative, depressive or positive symptoms. This variation in the findings could be due to a number of factors that are thought to possibly affect DST results, including severity of illness, age, gender, stress level, medication use and plasma DEX levels. This review did not find any significant effects of medication on DST outcome, with 29.4% of patients who were drug free for >2 weeks non-suppressors compared with 25.5% of medicated patients. The DST studies did, however, provide some evidence that non-suppression rates may vary over time in individual patients and also change with acute response to treatment. This is evidenced by studies where the DST was performed on hospital admission while patients were acutely psychotic and again after acute treatment with antipsychotic medications. All these studies showed reductions in the non-suppression rate at the follow-up DST. However, it is possible that this reduction in non-suppression rates was caused by reduction in symptoms and the likely accompanying reduction in stress during treatment, or possibly as a direct result of antipsychotics. However, the antipsychotics used were all first-generation drugs which, as previously stated, do not appear to have a direct effect on cortisol secretion.

There are three previously published reviews of the DST in schizophrenia. In a meta-analysis, Sharma et al. (1988) reported a non-suppression rate of 19% compared with 51% in major depression and 7% in controls. This meta-analysis applied different inclusion criteria to the present analysis: all studies had to include both depressed and schizophrenia patients, but the dose of DEX used in the DST could be 0.5, 1.0 or 2.0 mg. The meta-analysis reported by Yeragani (1990) found a non-suppression rate of 26.4% in schizophrenia versus 5.0% in controls. Tandon et al. (1991), in a summary meta-analysis, found a DST non-suppression rate of 36% in the drug-free state and 20% in the medicated state. Several other variables may have also have affected the results of these and the present analyses. For example, the lack of a control group to establish the cortisol level cut-off for the assay used could account for some of the variability in results in many studies. Furthermore, blood levels of DEX were rarely measured to ensure compliance or to investigate the effects of different blood levels of DEX on outcome.

In contrast to the large numbers of patients with basal cortisol measures, few studies have measured basal levels of other components of the HPA axis. CRH levels were only measured in five studies, all in CSF. In only one of these (Banki et al., 1987) was there any evidence of increased basal levels of CRH, although this was largely due to extremely high levels in three individuals. Furthermore, it is unclear if CSF CRH accurately represents the concentration of CRH in the hypophyseal portal system.

The studies measuring basal ACTH produced mixed results. Statistically significantly elevated ACTH was reported in only four studies (Brunelin et al., 2008; Kaneda et al., 2002; Ryan et al., 2004a; Walsh et al., 2005). Although the study reported by Brambilla et al. (1984) found no significant difference in basal ACTH level, 14/37 (38%) schizophrenia patients had a basal ACTH level above the range of the control group, providing more evidence that at least some schizophrenia patients have elevated ACTH levels. In the Brunelin et al. (2008) and Kaneda et al. (2002) studies increased ACTH was not matched by increased basal cortisol level, but in Ryan et al. (2004a) and Walsh et al. (2005), both of which were studies in first-episode, drug-naive patients, significantly elevated ACTH and cortisol levels were found. Kudoh et al. (1997) reported significantly lower basal ACTH ($p < 0.05$) but similar basal cortisol in schizophrenia and controls. These data collectively suggest that, in some patients, the elevated cortisol levels commonly measured in schizophrenia may also be stimulated by a mechanism other than increased CRH and ACTH. Ryan et al. (2004b) have proposed a mechanism for elevated cortisol involving arginine vasopressin (AVP). In this study, although ACTH was elevated in schizophrenia patients, it was not correlated with cortisol, suggesting it had another cause. The AVP AUC from 13 : 00 to 16 : 00 was actually lower in schizophrenia patients than in controls ($p < 0.02$), but there was a significant positive correlation between plasma AVP and cortisol ($r = 0.66$, $\mathrm{df} = 10$, $p < 0.02$) and between the AUC AVP and AUC cortisol ($r = 0.68$, $\mathrm{df} = 10$, $p < 0.05$). The authors suggest this significant positive association of AVP with cortisol may be explained by the fact that AVP can directly stimulate cortisol release from the adrenal cortex (Guillon et al., 1995) and therefore, in these patients, may have been responsible for hypersecretion of cortisol. Other studies have also reported a lack of association between ACTH and cortisol level in schizophrenia. Breier et al. reported no correlation between cortisol and ACTH, either during metabolic stress induced by the effects of 2-deoxy-D-glucose (which reduces glucose level) (Breier et al., 1988b), or psychological stress induced by a lumbar puncture procedure (Breier et al., 1988a).

Evidence is accumulating of other factors that may significantly affect the integrity and function of the HPA axis and therefore significantly influence outcomes in these studies. Some of these factors are particularly applicable to people with schizophrenia. For example, HPA axis function may be influenced by exposure to maternal stressors such as foetal malnutrition (Phillips and Jones, 2006) and psychological stress experienced by the mother during pregnancy (Glover et al., 2009) in a process termed foetal programming. These stressors may be expressed as a low birth weight or minor physical anomalies in the infant. Studies have demonstrated that low birth weight is associated with enhanced HPA axis and autonomic response to experimentally induced

psychological stress (Phillips and Jones, 2006). Schizophrenia is an illness associated with low birth weight (Cannon et al., 2002) and an increased incidence of minor physical anomalies (Compton and Walker, 2009), which may indicate increased exposure to a variety of maternal stressors. As these factors are more common in people with schizophrenia, they may have a greater influence on HPA function in schizophrenia patients and may contribute to the differences in HPA function seen between patients with schizophrenia and controls, as well as accounting for some of the variation in HPA function within the schizophrenia population. This potential is illustrated by Mittal et al. (2007) who demonstrated that schizotypal adolescents express significantly more minor physical anomalies than normal controls, and that these predict cortisol elevation.

Another factor is childhood trauma, which is associated with sensitization of the stress response, glucocorticoid resistance, increased CRH activity, immune activation and reduced hippocampal volume (Heim et al., 2008). Several studies have directly illustrated the effect of childhood trauma on HPA axis function. In a study of female youths maltreated during childhood (e.g. physical, sexual and emotional abuse), a blunted cortisol response to the Trier Social Stress Test was found compared with controls (MacMillan et al., 2009). Elzinga et al. (2008) also measured the cortisol response to the Trier Social Stress Test in people exposed to various levels of adverse life events such as emotional, physical or sexual abuse but with similar baseline cortisol levels. A significant blunted cortisol response was found in individuals with a history of adverse life events compared with individuals with no such events. This finding was primarily driven by the result in men.

Childhood trauma has been shown to be predictive and probably causal in the development of psychosis (Read et al., 2005; Shevlin et al., 2008), and it is therefore reasonable to assume that differences in the frequency and severity of childhood traumas in the schizophrenia populations studied could also explain some of the variance in the results. The potential for such an effect was seen in a recent study. Mondelli et al. (2010) found a significant negative correlation between the number of stressful life events and cortisol level ($r = -0.36$, $p < 0.014$) in first-episode, psychotic patients including schizophrenia and schizophreniform disorder. The control group, as expected, had a positive correlation between the number of stressful life events and cortisol level ($r = 0.42$, $p < 0.013$). The authors hypothesized that the unexpected negative correlation in psychotic patients may be explained by the excessive load of stressful life events experienced in this patient group. Stressful life events were experienced on average at around three times the rate in the psychotic cohort compared with the controls, and 85.7% of the psychotic patients had experienced a childhood trauma compared with 38.7% of controls. Furthermore, patients with post traumatic stress disorder (PTSD) caused by the extreme stress of physical or sexual abuse (that normally begins in childhood) show cortisol hyposecretion (Meewisse et al., 2007), suggesting that some forms of extreme stress may decrease HPA axis activation. In the Mondelli et al. study (2010), patients in the top 20th percentile for the number of stressful life events had similar cortisol levels as healthy controls, and it could therefore be that variations in exposure to extreme childhood trauma may account for some of the variation seen in the outcomes of the basal cortisol studies included in this review.

This systematic review found evidence in four studies that basal cortisol was significantly lower in schizophrenia patients than controls. CSF cortisol was measured in the study reported by Gattaz et al. (1985). Drug-free schizophrenia patients were found to have significantly lower cortisol than the control subjects who had non-specific neurological symptoms such as headache or dizziness. Wik (1995) studied newly admitted schizophrenia patients whose baseline cortisol was similar to controls. After 5–6 weeks of treatment with sulpiride or chlorpromazine, mean cortisol level was significantly lower than in the control group ($p < 0.001$). The authors concluded that the reduction of cortisol was caused by the antipsychotics, but patients also presumably had a reduction in symptoms and it is therefore not possible to conclude this with any confidence. It is also quite possible that following antipsychotic treatment, patients reverted to their symptom and stress-free basal cortisol levels, which were lower than those of the control group.

In a study by Monteleone et al. (1994), lower basal cortisol was consistently reported in a cohort of schizophrenia patients compared with controls in each of November, February and May. These patients had received chronic treatment with first-generation antipsychotics but were still symptomatic (mean SAPS score across the three timepoints approximately 40, and SANS score approximately 37). The other study reporting significantly lower basal cortisol in schizophrenia patients (Taherianfard and Shariaty, 2004) also found consistent evidence for reduced cortisol level. Cortisol was measured at three time points: in the drug-free state on admission to hospital, during treatment with antipsychotics, and on recovery. Cortisol level was significantly lower than in the control group at all three time points and did not change significantly from baseline at any time point. No information was given about the level of symptoms in these patients, but the findings suggest that some schizophrenia patients may experience hyposecretion of cortisol even when symptomatic and, as suggested by Mondelli et al. (2010), this could possibly relate to high exposure to significant stressors earlier in life. Of interest, a study reported by Mason et al. (1986) found that the low levels of cortisol in patients with paranoid schizophrenia were similar to those in patients with PTSD. Furthermore, these were significantly lower than in patients with bipolar disorder, depression or undifferentiated schizophrenia, although there was no non-psychiatric control group. The authors suggest that this low cortisol level may be maintained by a paranoid system of adaption, as also seen in the small study by Sachar (1970). These hypotheses may also explain the finding from many studies of no significant difference in cortisol level between patients and controls. This finding was reported even where patients were acutely ill and admitted to hospital where an increased level of cortisol might be expected (for example, Duval et al., 2003; Strous et al., 2004; Wik, 1995). It is conceivable, given the evidence from Mondelli et al. (2010), that some patients with schizophrenia who have experienced significant levels of life stress or perhaps childhood trauma may actually hyposecrete cortisol. In many studies where the schizophrenia cohort would

have included such patients, this would effectively reduce the mean cortisol level and therefore may explain why many studies found no significant differences in basal cortisol level between schizophrenia patients and controls. One small study gives credence to this hypothesis but needs replication in a larger cohort. Braehler et al. (2005) reported that schizophrenia patients who had experienced childhood trauma tended to have lower 24-h salivary free cortisol than patients with low levels of childhood trauma ($p = 0.011$). Cortisol was significantly lower in the childhood trauma group in the first hour after wakening, and was significantly negatively associated with emotional and sexual abuse. This study could not be included in the systematic review as it did not include any non-psychiatric controls.

CRH test and DEX/CRH test

Few studies have measured the response of the HPA axis to CRH in schizophrenia patients. The CRH test has only been reported once in drug-free and medicated patients with schizophrenia and results did not differ from controls, suggesting an intact HPA axis function (Roy et al., 1986). However, this study was small ($n = 9$) and patients showed various levels of psychosis. There was a trend towards a negative ACTH response with psychosis rating ($r = -0.42$, $p < 0.1$), suggesting ACTH response may be blunted in a more uniformly psychotic cohort. More studies using the CRH test are needed before any firm conclusions can be drawn.

The DEX/CRH test is thought to be more sensitive to subtle HPA system changes than the DST, but only one study reporting results of the DEX/CRH test in schizophrenia patients could be included in this review. Lammers et al. (1995) demonstrated that following pre-treatment with DEX, schizophrenia patients released more cortisol in response to CRH than controls. This was particularly so in drug-free patients who had higher BPRS scores than in medicated, less severely ill patients. Like the analysis of basal cortisol and DST, this suggests that illness phase may influence cortisol secretion. However, it is not possible to determine if reduction in cortisol secretion was related to lower levels of symptoms or the use of medication, as many of the medicated patients were taking clozapine, a drug known to have a direct effect on cortisol secretion. This study suggests that the mechanism of cortisol hypersecretion in these patients may be due, in part, to impaired negative feedback mechanisms, since this occurred following DEX. Of note, the cortisol response was increased in patients despite no significant difference in ACTH AUC between patients and controls over the course of the test, suggesting an explanation other than increased ACTH for the increase in cortisol, which may agree with the findings of Ryan et al. (2004b) and Breier et al. (1988a, 1988b).

Psychological stress and HPA axis response in schizophrenia

Since psychological stress may be important in the development and course of schizophrenia, studies that measure the reaction to psychological stress could be important in understanding how environmental factors contribute to pathogenesis of the disease. Studies measuring HPA axis response to psychological stress in schizophrenia patients produced consistent results, demonstrating a blunted ACTH and cortisol response to stress. The results were the same in drug-free, medicated, acutely psychotic and more chronic patients, suggesting these factors did not affect the outcomes of the studies. Where heart rate and mean arterial pressure were measured, increases in schizophrenia patients were similar to those in controls, indicating that patients found the tests stressful and that the physical response to stress was intact. A variety of explanations have been suggested for these results. Breier et al. (1988a) suggested that the blunted ACTH and cortisol stress response may partly be due to the significant negative correlation between the levels of psychosis and stress-induced increases in ACTH, i.e. the greater the psychosis, the lesser the increase in cortisol. They suggest it is possible that cognitive and/or neurobiological processes associated with severe psychosis have a disruptive effect on mechanisms involved in mounting a neuroendocrine stress response. In the study reported by Jansen et al. (2000), the cortisol response in schizophrenia patients to a physical stress, exercise, was not different from controls, and they suggest the blunted cortisol response to a psychological stress could be due to the different mechanisms of HPA axis activation to different types of stress. They cite evidence that physical stressors invoke a response via CRH and, as described in this review, CRH function appears relatively normal in schizophrenia patients, hence the normal stress response to exercise. Psychological stress stimulates the HPA axis via AVP (Romero and Sapolsky, 1996) which may be diminished in schizophrenia patients (Marx and Leiberman, 1998), resulting in a blunted cortisol response to psychological stress. The hypothesis proposed by Ryan et al. (2004b), that AVP may be responsible for hypersecretion of cortisol in first-episode patients via its ability to stimulate cortisol release directly from the adrenal gland, is seemingly at odds with this. They too found a reduction of AVP compared with controls, although the effects of AVP would have been augmented by the increased level of ACTH seen in their patients, which together could have accounted for the increased cortisol level.

Jansen et al. (2000) also suggest that the impaired stress response may be due to differences in coping strategies used by people with schizophrenia compared with controls. They found that schizophrenia patients used more passive and avoidance strategies compared with controls, which may invoke a different biological stress response. In the study reported by Brenner et al. (2009), although there was a trend towards lower cortisol secretion during psychological stress, it was suggested that cortisol secretion may just be delayed. This is based on the observation that cortisol levels were significantly lower at one time point during the study but were subsequently similar, suggesting the cortisol response was initially delayed but ultimately caught up. This group proposes that this could be due to impairment in executive functions where patients were less able to think ahead before the task, and therefore the stress associated HPA axis response was delayed. This view may be supported by

evidence from Gaab et al. (2005) who found that anticipatory cognitive appraisal of acute stressors explained up to one-third of the variance observed in cortisol response to stress. This cognitive appraisal could, of course, be impaired in schizophrenia patients. Brenner et al. (2009) also suggest that physiological differences in the HPA axis such as a hypoactivity could explain the delay in cortisol response. Hypofunction of the HPA axis during stress tests was also demonstrated by MacMillan et al. (2009) and Elzinga et al. (2008), in studies that found a blunted cortisol stress response to psychological stress in patients previously exposed to significant life stress. It is possible that in the schizophrenia cohorts studied, the rate of exposure to significant life stressors may have been greater in patients than in controls.

HPA axis function in schizophrenia: Implications for physical health and mortality

It is beyond the scope of this review to give detailed explanations of the role of stress and the HPA axis in the development of physical illness and premature mortality. Many excellent articles are already available, and the reader is referred to Benarroch (2005), Kyrou and Tsigos (2009), and Rosmond (2005) for the role of the HPA axis in metabolic and cardiovascular disease, Juster et al. (2010) for chronic stress, allostatic load and their impact on health, and Heim et al. (2000) and Raison and Miller (2003) for reviews of hypofunction of the HPA axis and physical health.

Figure 1 shows how the stress cascade can lead to physical ill health. Put simply, the HPA axis is a crucial system in maintaining homeostasis and adapting to the environment; it achieves this largely through the secretion of cortisol with subsequent effects on target organs. Prolonged exposure to high levels of cortisol can increase the risk of coronary heart disease by inducing central obesity, insulin resistance and lipid abnormalities (Rosmond, 2005).

A recent, large cross-sectional cohort study in patients with type 2 diabetes also found that elevated plasma cortisol levels were significantly associated with raised fasting glucose and total cholesterol levels after adjusting for possible confounders. Raised cortisol levels also increased the prevalence of ischaemic heart disease independently of conventional risk factors (Reynolds et al., 2010). Cortisol also plays an important anti-inflammatory role by inhibiting the immune activation caused by acute stress. However, prolonged exposure to cortisol may render the immune system insensitive to its anti-inflammatory effects via glucocorticoid receptor resistance, allowing the development of a chronic inflammatory state

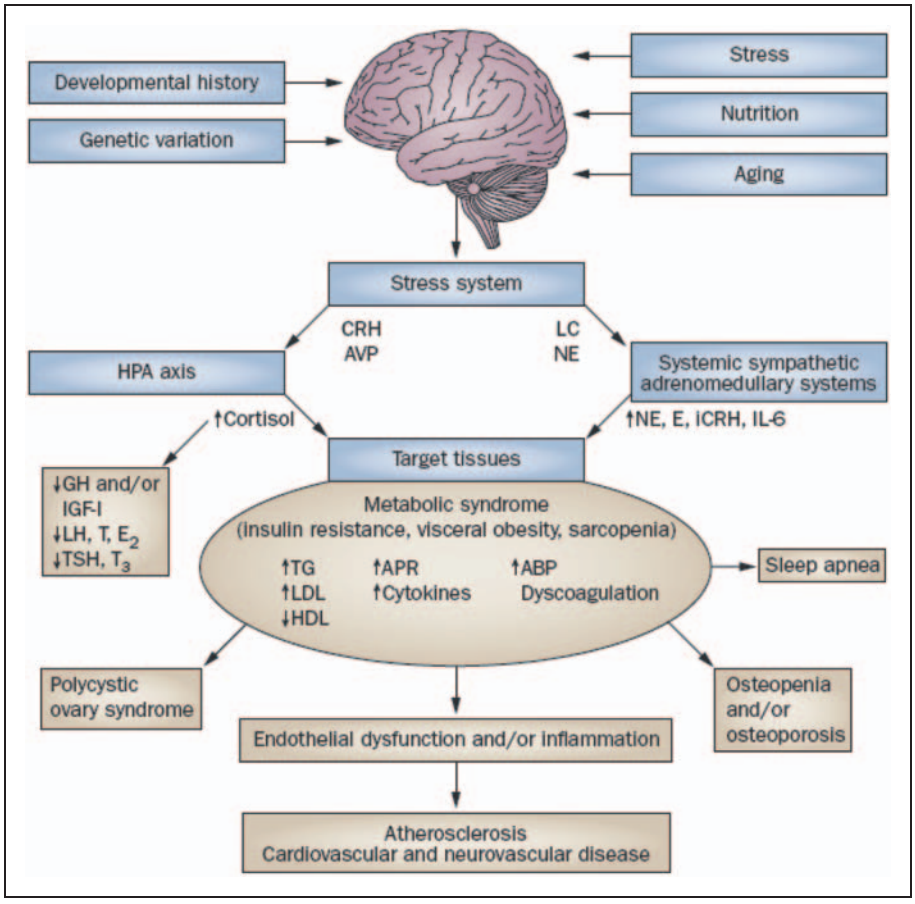

Figure 1. Reprinted by permission from Macmillan Publishers Ltd. Chrousos GP. *Nat Rev Endocrinol* 5: 374–381. Copyright 2009.

characterized by high levels of inflammatory cytokines such as IL-6 (Miller et al., 2009). A pro-inflammatory state is evidenced in schizophrenia patients by the increased pro-inflammatory cytokines found in patients with schizophrenia including IL-6 (Potvin et al., 2008). An increase in IL-6 is associated with an increased risk of atherosclerosis and type 2 diabetes (Pickup, 2004), and so could plausibly have a role in the increased incidence of these diseases in schizophrenia.

Similar effects on immune function may also be seen with an underactive HPA axis, when too little cortisol at times of stress may allow the acute immune response to continue unopposed (McEwen, 1998), also resulting in increased inflammation. These two scenarios are both plausible in schizophrenia patients given the evidence found in this systematic review. Both prolonged, elevated cortisol and a blunted cortisol response to psychological stress have been demonstrated, even in the presence of an increased physical response to psychological stress. There may also be a subset of patients who have experienced significant childhood traumas with a general hypofunctioning of the HPA axis. Depending on the pattern of symptoms and treatment, exposure to the stressful effects of psychosis may last many weeks or even months. In a chronic illness such as schizophrenia, which is characterized by repeated symptom exacerbation, over (or sometimes under) exposure to cortisol may continue for many years. It is thus reasonable to conclude that over many years the pattern of HPA function in schizophrenia patients probably contributes to the increased levels of central obesity, insulin resistance, lipid disturbance and premature mortality from cardiovascular disease found in this population. In schizophrenia there is evidence of increased central obesity (Ryan et al., 2004a; Thakore et al., 2002) and insulin resistance (Spelman et al. 2007; Venkatasubramanian et al., 2007) from the first episode in drug-naive patients. These features are also commonly found in patients with chronic schizophrenia (McEvoy et al., 2005), although other factors such as lifestyle and treatments are also likely to contribute. It could also be hypothesized that patients with the highest and most prolonged overexposure to high cortisol levels may experience the more severe effects of cortisol overexposure. Therefore it is possible, given the relationship of cortisol levels with symptoms, course of illness and treatments, that patients with different types of schizophrenia experiencing different symptom patterns and treatments may experience a different pattern of ill-health related to HPA axis function. There would also likely be a strong influence from patients prior exposure to severe stressors, both pre and postnatal, given the previously described evidence that in utero stress, birth weight and childhood trauma significantly influence HPA axis function into adult life.

Another important role of cortisol in mortality may be the association between cortisol and suicide risk. Suicide is the leading cause of premature mortality in younger schizophrenia patients (Mortensen and Juel, 1993), and therefore this may be of particular relevance in first-episode schizophrenia and the early years of schizophrenic illness. Several studies in depressed patients have found an association of DST non-suppression (Jokinen and Nordstrom, 2009a; Jokinen et al., 2007; Mann et al., 2006) and suppression with suicide or suicide attempt (Black et al., 2002). Hypoactivity of the HPA axis (Lindqvist et al., 2008; Pfennig et al., 2005) has also been associated with suicide attempt. In schizophrenia, Jones et al. (1994) and Plocka-Lewandowska et al. (2001) found an association of non-suppression in the DST with suicide attempt, while Lewis et al. (1996) did not. De Luca et al. (2010) recently reported an association of HPA axis genes with suicide attempt in schizophrenia. These data suggest that HPA axis genes influence the stress reactivity of an individual and therefore the likelihood of that individual to develop a mental disorder and to attempt suicide. Finally, cortisol itself has also been demonstrated to be a predictor of mortality in patients with depression, although there is no current evidence that this is the case in patients with schizophrenia. Preliminary evidence in two studies of people with depressive illness suggests that HPA axis dysfunction may be a risk factor for cardiovascular mortality. Coryell et al. (2008) found that higher maximum post-DEX cortisol levels predicted deaths due to cardiovascular causes, and Jokinen and Nordstrom (2009b) found that higher baseline serum cortisol and DST non-suppression predicted cardiovascular disease death, particularly in male patients. One previous study found no such relationship (Coryell et al., 2006).

Strengths and weaknesses of this review

A major strength of this review is its systematic nature: it includes all of the published literature to date found by our search strategy. Although previous reviews have been published, none employed a systematic search strategy of HPA function in schizophrenia. We also included a number of study types in order to fully understand and accurately describe HPA function in schizophrenia, including basal measures, studies using various HPA axis probes and studies examining HPA axis response to psychological stress. We only included studies where schizophrenia was diagnosed using recognized structured interviews in order to exclude other psychoses which may have a different pattern of HPA function. We did, however, include other diagnoses where they contributed less than 10% of the overall sample. For studies using the DST, we only included those that utilized a standard DST methodology. For studies of psychological stress tests, we only included studies that used reliable methods of invoking a stress response.

A weakness of this review is that it is not a meta-analysis. In theory this would be a useful way to assess whether cortisol levels are different between schizophrenia patients and controls. However, the number of potential confounders makes this a very difficult, and possibly misleading, task. The time of cortisol measure was not standardized between studies, making direct comparisons between studies invalid. Standard mean differences between schizophrenia patients and controls could have been examined, but these may differ by time of day as cortisol secretion is not uniform throughout the day and circadian rhythm may be disrupted in schizophrenia. Also, the number of other confounders both recognized, such as medication use and phase of illness, and others unknown, would have made this a very difficult task producing a possibly misleading outcome. We did not examine the effects of age, gender or genetics on HPA axis function, and it is likely these may explain some of the variation in

results. It is also possible that some studies excluded from this systematic review would add useful information to the discussion of HPA axis function in schizophrenia.

Conclusions

Despite the heterogeneity of outcomes from the studies reviewed, there is evidence that people with schizophrenia experience periods of heightened cortisol secretion. This consistently occurs at the first episode but also occurs in some chronic patients with more stable clinical features. The variation in results may be explained by varying symptoms of illness as well as by medication use and exposure to other environmental factors known to influence HPA axis function. Some patients with schizophrenia may also experience low cortisol levels under certain conditions. This is particularly evidenced by a blunted cortisol response to a psychological stress test but may also be the case in acutely ill patients, as many studies found no evidence of elevated cortisol in psychotic patients admitted to hospital where a stress response would reasonably be expected. In view of the strong evidence in the general population, this pattern of HPA axis function is also likely to significantly contribute to the poor physical health (particularly metabolic and cardiovascular) and premature mortality seen in patients with schizophrenia.

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Conflict of interest

AJB is an employee of Eli Lilly and Company Ltd. This paper has been written by the named authors without editorial assistance.

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