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Assessment of serum cortisol, thoughts of death, and loss of pleasure in patients with schizophrenia: a correlative study

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Context
The hypothalamic–pituitary–adrenal (HPA) axis seems dysregulated in schizophrenic patients, but the underlying mechanisms are unknown; yet recent evidence indicates that systemic cortisol metabolism influences blood cortisol levels and HPA axis functioning.

There has been a recent increase in interest in anhedonia research. Linkages to schizophrenia and the underlying neurobiology are still not well understood. There is clear evidence that the activity of certain neurobiological systems has a role in the pathophysiology of suicidal behavior and this includes hyperactivity of the HPA axis.

Objectives
The objectives of this work were to examine whether there is an increased activity of HPA axis in schizophrenic patients, and to detect the presence of an association between the level of plasma cortisol and thoughts of death and anhedonia in the disorder.

Setting and design
Twenty patients diagnosed with schizophrenia were studied in comparison with 20 controls.

Patients and methods
All patients were assessed through Present State Examination, 10th revision. The Snaith Hamilton Pleasure Scale was used to assess anhedonia, and Beck's Suicidal Ideation Scale was used to quantify suicidal intention. In addition, The Positive and Negative Syndrome Scale was also used. Blood samples were collected from all patients to assess plasma cortisol level in the morning and evening.

Statistical analysis
Collected data in this study were analyzed using the statistical package for the social sciences (version 15).

Results
There were increased levels of morning and evening cortisol in schizophrenic patients. Thoughts of death were positively associated with elevated morning cortisol.

Conclusion
Schizophrenic patients have higher cortisol levels in comparison with controls, suggesting hyperactivity of the HPA axis in the disorder. Anhedonia predicts suicidal tendencies in schizophrenia; the higher the anhedonia, the higher the suicidal ideations.

Keywords:
anhedonia, cortisol, hypothalamic pituitary adrenal, schizophrenia, suicidality

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Introduction

The hypothalamic–pituitary–adrenal (HPA) axis seems dysregulated in schizophrenia, but the underlying mechanisms are unknown (Steen *et al.*, 2011). Anhedonia, which is defined as the decreased capacity to experience pleasure, is a common treatment-resistant feature of schizophrenia that is often included among the negative symptoms of this disorder (Horan *et al.*, 2006) and it has often been associated with disease chronicity and poor treatment outcome (Putnam *et al.*, 2008).

Since the time of Kraepelin and Bleuler, alterations in emotional experience and expression have been recognized to represent a core feature of schizophrenia and play a central role in two prominent negative symptoms: flat affect and anhedonia (Oorschot *et al.*, 2013).

The relationship between HPA axis and anhedonia was studied in an early human study by Berenbaum and Connelly (1993), who found that real-life acute stressors, including military training and final examinations, reduced self-reported pleasure. Furthermore, in a controlled laboratory setting, Bogdan and Pizzagalli (2006) reported that an acute

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stressor blunted reward responsiveness, specifically participants' ability to modulate behavior as a function of rewards.

O'Carroll *et al.* (1996) defined suicidal ideation as 'any self-reported thoughts of engaging in suicide-related behavior' and McGirr *et al.* (2010) stated that dysregulation of the HPA axis is hypothesized to play a role in increasing susceptibility to suicidal behavior.

Van *et al.* (2000) emphasized that there is clear evidence that the activity of certain neurobiological systems has a role in the pathophysiology of suicidal behavior; this includes hyperactivity of the HPA axis. High levels of cortisol are associated with increase in suicidal risk (Guzmán *et al.*, 2011). Yet, other studies have not found such an association (Pitchot *et al.*, 2003; Jokinen *et al.*, 2007).

Patients and methods

Study design

This study was conducted on a nonrandomized purposive sample of 20 patients with schizophrenia, diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (American Psychiatric Association, 2000), in comparison with 20 controls. Patients were selected from the outpatient clinic of the Psychiatry Department, Kasr El Aini Hospital, Cairo University.

All patients in the study were asked to provide written informed consent before starting the assessment.

After the initial diagnosis a morning cortisol sample was taken from the participants and they were given an appointment to come in the evening for the evening cortisol sample and undergo psychometric assessment.

Controls

Twenty individuals matched in age and sex without a past history of any psychiatric disorders or a first-degree relative with psychiatric disorders were taken as controls.

Inclusion criteria

Individuals of either sex, aged 19–50 years, with schizophrenia and not receiving any medications, and who had undergone substance and/or electroconvulsive therapy in the last 6 months were eligible for participation in the study.

Exclusion criteria

Patients who refused to participate, those aged below 19 years or above 50 years, patients who did not complete the required tests, those with any medical disorder that may affect the cortisol level (e.g. Cushing's syndrome, pheochromocytoma, etc.), substance abusers, pregnant women or women taking oral contraceptive pills, patients receiving corticosteroid therapy, and those with any major chronic disabling disease (e.g. stroke, systemic lupus erythematosus, etc) were excluded from the study.

Assessment tools

(1) Full psychiatric examination using Present State Examination, 10th revision, of the Schedules of Clinical Assessment in Neuropsychiatry: Sabry N (2009) study illustrates that the short Arabic version of the Present State Examination is a reliable interview with adequate levels of internal consistency.
(2) General medical examination: to detect and exclude any medical condition.
(3) Psychometric assessment:
    (a) Snaith Hamilton Pleasure Scale Snaith *et al.* (1995) (SHAPS): The Arabic version was obtained from Thomas*et al.* (2012).
    (b) Beck's Suicidal Ideation Scale (SIS) (Beck*et al.*, 1979): It consists of 19 items that evaluate three dimensions of suicide ideation: active suicidal desire, specific plans for suicide, and passive suicidal desire.
    (c) Positive and Negative Syndrome Scale (PANSS): It comprises four scales measuring positive and negative symptoms, their differences, and general severity of illness (Kay*et al.*, 1987).
(4) Laboratory tests and specimen collection:

Blood samples were collected between 8 and 9 a.m. and between 8 and 9 p.m. from all participants to assess plasma cortisol levels.

Blood was drawn into plain tubes, preserved frozen at −4°C, and then separated for subsequent measurement of cortisol in serum with IMMULITE and IMMULITE 1000 cortisol (SIMENS (2007): Simens Medical Solutions Diagnostics. 5210 Pacific Concourse Drive. Los Angeles, CA 90045-6900, USA, PILKCO-11) analyzers. The volume required was 10 µl of serum. Reference ranges for cortisol vary from laboratory to laboratory but are usually within the following ranges for blood: 8–9 a.m., 5–38 µg/dl; 8–9 p.m., 3–15 µg/dl (Foster and Dunn, 1974).

Statistical analysis

The data collected in this study were analyzed using the statistical package for the social sciences (version 15; SPSS Inc., Chicago, Illinois, USA). Qualitative

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variables were described as number and percentages and quantitative variables as mean and SD.

χ^2-Test

This is a test of statistical significance used for comparison between different groups in which qualitative variables are expressed as percentages when comparing categorical data. The exact test was used when the expected frequency is less than 5.

Mann–Whitney U-test

A statistical test for comparison of numerical variables between the study groups was performed for independent samples when comparing two groups. *P* values were used to indicate the level of significance ($P<0.05$ was considered significant). Linear relationships were examined with Pearson's correlation coefficient.

Results

Sample characteristics

The mean age of the patients was 30.85±7.76 years and that of controls was 32.50±11.19 years. Sixty-five percent of patients were male, compared with 40% of the sample in the control group. Seventy percent of the patients were single, in contrast to 15% of the controls.

Clinical assessment

In the schizophrenic group, none of the patients had an acute onset of illness; 15% had subacute onset and 85% had a gradual onset. All patients had a progressive course of illness. Duration of the psychiatric illness ranged between 7 and 120 months, with a mean of 47.55±35.55 months.

Ninety percent of the patients had no family history of psychiatric disorder, whereas 10% had a family history of psychiatric illness similar to that of the patient.

Psychometric assessment tools

Forty-five percent of the patients had auditory hallucinations, 45% had delusions of persecution, and 50% had delusions of reference, whereas none of the controls had any psychotic symptoms ($P=0.000$) (Table 1).

The mean positive symptoms score in PANSS was 22.96.64, the mean negative symptoms score in PANSS was 28.65±5.68, the mean general psychopathology score in PANSS was 38.60±8.45, and the mean total score in PANSS was 90.55 ±17.34 (Table 2).

Table 1 Symptoms under sections 9 (perceptual disorders), 10 (thought disorder and replaced well), and 11 (delusions) in Present State Examination

PSE sections 9, 10, and 11	Schizophrenia [*n* (%)]	Control [*n* (%)]
Auditory hallucinations	9 (45)	0 (0.0)
Thought possession	3 (15)	0 (0)
Delusions of being spied upon	3 (15)	0 (0)
Delusions of persecution	9 (45)	0 (0)
Delusions of reference	10 (50)	0 (0)
Delusions of grandeur	1 (5)	0 (0)
No symptoms	0 (0)	20 (100)
P value	0.000	

PSE, Present State Examination.

Table 2 Positive and Negative Syndrome Scale results in the schizophrenia group

	Mean±SD
Positive symptoms	
Total of positive scale	22.9±6.64
Negative scale	
Total of negative scale	28.65±5.687
General psychopathology	
Total of general psychopathology scale	38.60±8.450
Total PANSS	90.55±17.34

PANSS, Positive and Negative Syndrome Scale.

Table 3 Risk of suicide according to Beck's Suicidal Ideation Scale

	Schizophrenia [*n* (%)]	*P* value
Risk of suicide according to Beck's Suicidal Ideation Scale		
Low	0 (0)	0.500
Moderate	7 (35.0)	
High	13 (65.0)	

Table 4 Snaith Hamilton Pleasure Scale results

SHAPS	Schizophrenia
Mean	10.85
SD	2.32

SHAPS, Snaith Hamilton Pleasure Scale.

Table 3 shows that there was no statistically significant difference between patients regarding suicide risk.

Table 4 shows that the mean SHAPS score was 10.35 ±2.56.

Table 5 shows that there was no statistically significant difference between patients and controls regarding cortisol level.

Table 6 shows that there was a positive correlation between SHAPS score and positive symptoms score ($r=0.422$). The *P* value was not significant ($P\geq0.064$).

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Table 5 Serum cortisol level (morning and evening) in the study sample

Groups	Serum cortisol level morning	Serum cortisol level evening
Schizophrenia		
Mean	18.155	8.03
SD	10.7384	4.292
Minimum	4.0	2
Maximum	38.8	18
Controls		
Mean	10.15	3.43
SD	9.80	1.38
Minimum	5.3	1
Maximum	29.5	7
P value	0.060	0.373

Table 6 The correlation between Snaith Hamilton Pleasure Scale, Positive and Negative Syndrome Scale, and serum cortisol level in the schizophrenia group

Spearman's ρ	SHAPS score
Positive symptoms score	
Correlation coefficient	0.422
P value	0.064
Negative symptoms score	
Correlation coefficient	0.157
P value	0.508
General psychopathology score	
Correlation coefficient	0.300
P value	0.199
Serum cortisol level morning	
Correlation coefficient	0.276
P value	0.239
Serum cortisol level evening	
Correlation coefficient	0.093
P value	0.698

SHAPS, Snaith Hamilton Pleasure Scale.

Table 7 The correlation between Beck's Suicidal Ideation Scale, Positive and Negative Syndrome Scale, serum cortisol level, and Snaith Hamilton Pleasure Scale in the schizophrenia group

Spearman's ρ	Beck's Suicidal Ideation Scale score
Positive symptoms score	
Correlation coefficient (*r*)	0.371
P value	0.108
Negative symptoms score	
Correlation coefficient	0.161
P value	0.497
General psychopathology score	
Correlation coefficient	0.142
P value	0.549
Serum cortisol level morning	
Correlation coefficient	0.502
P value	0.024
Serum cortisol level evening	
Correlation coefficient	0.227
P value	0.336
SHAPS score	
Correlation coefficient	0.473
P value	0.035

SHAPS, Snaith Hamilton Pleasure Scale. Assessment in Neuropsy.

Table 7 shows that there was a statistically positive correlation between Beck's SIS score and the level of cortisol in the morning (r=0.502) and a statistically positive correlation between Beck's SIS score and SHAPS score (r=0.473).

There was a positive correlation between Beck's SIS score and the positive symptoms score (r=0.371).

Discussion

This work was intended to study whether there was an increased activity of HPA axis in patients diagnosed with schizophrenia and to detect the presence of an association between the level of serum cortisol and thoughts of death and anhedonia in schizophrenia.

The mean age of the patients was 30.85±7.56 years. Middle-aged patients were selected to avoid the adolescence period with its possible endocrinal changes. Older patients above 50 years were excluded to avoid the higher level of diurnal cortisol secretion that advanced age can be associated with, as reported by Wrosch *et al.* (2008). Male patients represented the highest percentage (65%). The difference can be related to the higher number of male patients with psychotic disorders who seek or are brought by their families for psychiatric treatment and the small number of female patients presenting to the outpatient clinic; in addition, McGrath *et al.* (2004) found that female schizophrenic patients were more complaint to medications with better prognosis and lesser relapse rate compared with male schizophrenic patients.

Years of formal education ranged between 0 and 16 years, with a mean of 8.65±6.73 years, suggesting that the mean education of patients lies within the preparatory level.

In controls years of formal education were higher, ranging between 0 and 18 years, with a mean of 12.30±5.16 years. The significant deterioration in education in schizophrenic patients reflects the effect of the early onset of illness and the neurocognitive changes that leads to lack of motivation and academic deterioration that occur with schizophrenia (Strauss *et al.*, 2012).

Unemployment among patients was high, at 65%. We agree with Agerbo *et al.* (2004) that schizophrenia has a

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deteriorating effect on the cognitive aspect of the patients, which might decrease the chance of the patient to have or to continue in skilled or professional work. Also, the lack of interest to be regular in a certain job may be another contributing factor.

It was found that only 20% of the patients were married, whereas 70% of them were single and 10% were divorced. Individuals with schizophrenia are less likely than healthy control individuals to get married. This might be explained by the fact that unemployment rates are very high among schizophrenic patients (65% in this study) and hence they cannot afford the financial burden of marriage and raising children. The early onset of illness affects social skills and the ability to establish relationships, which may lead to a lack of emotional reciprocity between the two partners, as considered by Kebede *et al.* (2004) and Ponnudurai *et al.* (2006).

In schizophrenic patients, the mean cortisol level was 21.87±13.59 μg/dl for the morning sample and 9.26 ±6.90 μg/dl for the evening sample. In the control group, the mean was 10.15 1±9.8 μg/dl for morning cortisol and 3.43±1.38 μg/dl for evening cortisol.

A similar finding was noticed in the studies by Venkatasubramanian *et al.* (2010), Dessoki *et al.* (2013), and Sarhan *et al.* (2013), where there was elevated level of cortisol in the patient group compared with the control group. Strous *et al.* (2004) found that there were no statistically significant differences between the schizophrenic group and controls regarding cortisol levels.

Although the levels of cortisol in the morning and evening were elevated in schizophrenic patients in comparison with controls, we found no statistically significant difference between the three studied groups regarding serum cortisol in the morning and serum cortisol in the evening (P=0.060 and 0.373, respectively). In addition, cortisol levels were in the normal ranges for the reference laboratory. This indicates that the activity of the HPA axis differs in schizophrenic patients and that schizophrenic patients have pronounced disturbance in HPA axis activity.

In contrast, in the study by Taherianfard and Shariaty (2004) cortisol levels were significantly lower in schizophrenic patients than in controls. The lower steroid serum levels in schizophrenic patients could not be accounted for by age or medication intake. Thus, the current findings provide a strong support for the idea that abnormal steroid serum levels occur in schizophrenia and may be involved in the pathophysiological process of schizophrenia, at least in male schizophrenics. Yet the exact mechanism(s) are unknown.

According to Brenner *et al.* (2009) the lack of differences in levels of cortisol between schizophrenic patients and comparison healthy controls is not surprising as a blunted cortisol response has previously been reported in schizophrenic patients (Ristner *et al.*, 2004). This controversy regarding hormonal levels between this study and other studies might be attributable, at least in part, to a number of different demographic and clinical characteristics across studies, such as age, symptom severity, duration of illness of the patients enrolled in the studies, drug treatment (typical, atypical, and combinations), comorbid psychiatric disorder, and number of controls in relation to number of schizophrenic patients.

There was a positive correlation between SHAPS score and positive symptoms score in patients with schizophrenia. The reduced ability to experience pleasure, anhedonia, is a core feature of schizophrenia and has been proposed to be a possible indicator of the genetic tendency to develop this disorder. It was theorized that anhedonia is a feature of schizotypy (the personality disorder that emerges in individuals with a genetic vulnerability for schizophrenia) (Blanchard *et al.*, 2011). Anhedonia as a dimension of both negative and positive schizotypy involves social and interpersonal deficits, but is also associated with cognitive decline and disorganized speech, both of which fall into the category of positive schizotypy (Gooding *et al.*, 2001).

A finding similar to this work, that social anhedonia is elevated in positive schizotypy schizophrenia, was found in a study conducted by Horan *et al.* (2007).

There was also a significant positive correlation between delusions and cortisol levels in the morning and evening, consistent with the study by Keshavan *et al.* (1989). However, our findings were inconsistent with those of Tandon *et al.* (1991).

In addition, there was a positive correlation between cortisol level in the morning and total PANSS (P=0.020, r=0.567). This result was consistent with that of Sarhan *et al.* (2013), while being inconsistent with that of Hori *et al.* (2012), who found that total PANSS score was not significantly correlated with cortisol level.

We believe that these differences might be because these studies were heterogeneous in their methodology and

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outcomes, making interpretation of the results complex and variable. Variations in methods included the time of cortisol measurement and whether patients were medicated or drug free, symptomatic, or stable.

It was also found that there was a positive but not significant correlation between Beck's SIS score and positive symptoms score (P=0.108, r=0.371).

The results of the studies on positive symptoms of schizophrenia and suicidical tendencies were heterogeneous; positive symptoms are generally less often included among risk factors for suicide in schizophrenia. However, a number of studies have found that the active and exacerbated phase of the illness and the presence of psychotic symptoms, as well as paranoid delusions and thought disorder, are associated with a high risk for suicide. Suicides as a result of command hallucinations, although rare, have been reported in the literature (Kelly *et al.*, 2004; Pompili *et al.*, 2007).

Another study reported a significant negative association between delusions and suicide risk (Roos *et al.*, 1992). In this work there was no correlation between negative symptoms scale score and Beck's SIS score.

There are conflicting data on negative symptoms in general with no overall association with suicide risk (Hawton *et al.*, 2005). However, a protective association was found in a single study using a negative symptom scale, which also found a protective association for flat affect (Fenton WS., 2000).

Also, there was a statistically significant positive correlation between Beck's SIS score and the serum level of cortisol in the morning. As the level of cortisol increased in the morning, the suicidal thoughts became higher. This is consistent with the results of Płocka-Lewandowska *et al.* (2001), who found an association between suicidal behavior and cortisol level in schizophrenia, and all cortisol levels were significantly higher in patients with a history of suicide attempt.

Studies on the relation between suicidal behavior and HPA function often involve diagnostically heterogeneous populations but they suggest that there is an association between suicidal behavior and hyperactivity of the HPA axis. The two most consistent findings regarding the HPA axis relate to violence of attempts and eventual suicide completion (Fenton WS., 2000; McGirr *et al.*, 2010; Furczyk *et al.*, 2013).

De *et al.* (2010) found that genetic variation in HPA axis genes could be associated with suicidal behavior in schizophrenia, where a significant interaction between corticotropin-releasing hormone receptor type 1 and corticotropin-releasing hormone binding protein was linked to suicide attempts and the severity of suicidal behavior among schizophrenic patients. Yet other studies did not find an association between elevated cortisol level and dexamethasone supression test nonsuppression and suicide risk in schizophrenia (Lewis *et al.*, 1996; Oquendo *et al.*, 2003) were unable to find an association between suicidal behavior and plasma cortisol in their study.

A statistically significant positive correlation was found between Beck's SIS score and SHAPS score (P=0.035, r=0.473). The higher the severity of anhedonia, the more severe the suicidal ideation. This is similar to the finding of Orlova *et al.* (2011), who also found that anhedonia in schizophrenia is a risk factor for suicidal behavior. The suicidal behavior manifested itself with suicidal attempts more than with suicidal ideas. Suicidal attempts were impulsive and dangerous, with a high risk for life.

Conclusion

There are increased levels of morning and evening cortisol in schizophrenic patients; thoughts of death are positively associated with elevated morning and evening cortisol levels. Both anhedonia and suicide risk are high in schizophrenics, and anhedonia predicts suicidal tendencies in schizophrenia. The more severe the anhedonia, the higher the suicidal ideations.

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Conflicts of interest

There are no conflicts of interest.

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