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HPA axis in psychotic major depression and schizophrenia spectrum disorders: Cortisol, clinical symptomatology, and cognition☆

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ABSTRACT

The Hypothalamic Pituitary Adrenal (HPA) axis has been implicated in the pathophysiology of a variety of mood and cognitive disorders. Neuroendocrine studies have demonstrated HPA axis overactivity in major depression, a relationship of HPA axis activity to cognitive performance, and a potential role of HPA axis genetic variation in cognition. In schizophrenia differential HPA activity has been found, including higher rates of non-suppression to dexamethasone challenge and higher salivary cortisol levels, which have been a premonitory risk factor for conversion to psychosis in adolescents at risk for developing schizophrenia. The present study investigated the simultaneous roles HPA axis activity and clinical symptomatology play in poor cognitive performance. Patients with major depression with psychosis (PMD) or schizophrenia spectrum disorder (SCZ) and healthy controls (HC) were studied. All participants underwent a diagnostic interview and psychiatric ratings, a comprehensive neuropsychological battery, and overnight hourly blood sampling for cortisol. Cognitive performance did not differ between the clinical groups, though they both performed more poorly than the HC's across a variety of cognitive domains. Across all subjects, cognitive performance was negatively correlated with higher cortisol, and PMD patients had higher evening cortisol levels than did SCZ and HCs. Cortisol and clinical symptoms, as well as age, sex, and antipsychotic use predicted cognitive performance. Diathesis stress models and their links to symptomatology, cognition, and HPA function are discussed.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays important roles in normal response to stressors and in regulating somatic and brain functions throughout the natural circadian rhythm (Lupien and McEwen, 1997; Schatzberg and Lindley, 2008; Sudheimer et al., 2015; Watson and Mackin, 2009). The principal output of the HPA axis is the glucocorticoid, cortisol, which is secreted acutely in response to acute stress, but is also released according to a diurnal rhythm, with highest levels observed in the morning and lowest levels seen at approximately midnight (Schatzberg and Lindley, 2008).

The HPA axis has been implicated in several psychiatric disorders, particularly in relation to abnormal stress responses (Aas et al., 2011; Zorn et al., 2017). The distinct nature of these abnormalities and their relationships with disease etiology and outcomes, however, remain unclear. Baseline cortisol levels are seen in a circadian rhythm pattern of cortisol circulation. Compared to healthy controls, there have been mixed baseline cortisol findings in depressed patients. Some studies have shown normal baseline cortisol levels, while others found elevated baseline cortisol (Burke et al., 2005; Watson and Mackin, 2009). However, in psychotic major depression, baseline levels are consistently found to be elevated compared to both healthy controls and nonpsychotic depression (Contreras et al., 2007; Dalm et al., 2018; Keller et al., 2006; Watson and Mackin, 2009).

In patients with schizophrenia, most of the early work found no differences between individuals with schizophrenia and healthy controls in basal levels and in cortisol circadian rhythms (Roy et al., 1986; Rao et al., 1995), though more recent work has found hyperreactivity of the HPA axis in schizophrenia with basal levels higher in schizophrenia patients compared to controls (Breier and Buchanan, 1992; Walker et al., 2008). A meta-analysis showed that in just under half of the studies examined, patients with schizophrenia demonstrated significantly elevated mean baseline cortisol levels, while just over half of the studies showing no significant

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difference in cortisol levels compared to healthy controls (Bradley and Dinan, 2010). Furthermore, a small percentage of studies demonstrated significantly hypoactive HPA-axis function, that is, lower baseline cortisol, in patients with schizophrenia (Bradley and Dinan, 2010), while others have found that in schizophrenia patients, there tends to be elevated morning cortisol (Girshkin et al., 2014). In adolescents at risk of developing schizophrenia, there tends to be higher rates of dexamethasone non-suppression, indicative of elevated cortisol (Tandon et al., 1991). The literature on stress responsivity in schizophrenia is more consistent, with a pattern of consistently blunted cortisol levels in response to stressors (Bradley and Dinan, 2010; Brenner et al., 2009; Gispen-de Weid, 2000; Zorn et al., 2017), regardless of disease stage, chronicity, medications, and presence of active psychosis (Bradley and Dinan, 2010). A wide number of factors mediating cortisol levels have been discussed in the literature, including phase of illness, chronicity, environmental factors, stress vulnerability, medication usage, and clinical history (Carol and Mittal, 2015).

In addition to dysfunctional HPA activity, individuals with affective and psychotic disorders demonstrate cognitive inefficiencies that contribute to difficulties in treatment compliance and psychosocial and occupational function (Bora et al., 2009; Bora et al., 2012; Kaser et al., 2017; McIntyre et al., 2013; Rock et al., 2014). In psychotic affective disorders, cognitive findings show a pattern of difficulties in memory, executive functions, attention, processing speed, and working memory (Gomez et al., 2006; Reichenberg et al., 2008). However, when comparing patients with psychotic major depression to those with non-psychotic major depression, the former showed greater cognitive impairments in attention, cognitive inhibition, and verbal memory compared to non-psychotic depressed patients and healthy controls (Schatzberg et al., 2000; Gomez et al., 2006). In schizophrenia, the typical pattern of neuropsychological dysfunction lies in the domains of memory, executive functions, attention, and processing speed. Both psychotic depressed and schizophrenic patients demonstrate impaired cognition compared to healthy controls and have similar patterns of dysfunction (Bora et al., 2009; Reichenberg et al., 2008).

Cortisol has been shown to affect neurocognitive performance, with an inverted U-shaped dose-response curve with respect to the effect of cortisol on cognition (Lupien and McEwen, 1997). At certain concentrations, there tend to be positive effects on cognitive functions, whereas lower and higher concentrations of cortisol result in decreased cognitive performance (Holtzman et al., 2013; Lupien and McEwen, 1997). Investigation of the relationship between cortisol and neurocognitive function in depression revealed that elevated cortisol affects verbal memory and response inhibition, regardless of medication status (Gomez et al., 2009). Furthermore, PMD patients were specifically found to have elevated cortisol levels associated with worse cognitive performance, particularly for verbal and working memory (Gomez et al., 2006).

In schizophrenia spectrum disorders, studies have demonstrated impairments in verbal memory, attention, working memory, processing speed, and executive functions, including problem solving and cognitive inhibition (Bora et al., 2009; Reichenberg et al., 2008). Cortisol levels and verbal memory have been shown to be inversely correlated in schizophrenia, though the cortisol levels may be associated with more severe positive symptoms rather than attentional difficulties (Walder et al., 2000). Several studies, however, found that negative symptoms were related to worse cognition and increased brain abnormalities compared to patients with primarily positive symptoms, while patients experiencing primarily positive symptoms had less marked cognitive impairments (Andreasen et al., 1990; Basso et al., 1998; Mojtabai et al., 2000). This is of particular interest because several studies have correlated positive symptoms in schizophrenia with increased levels of cortisol (Coulon et al., 2016; Garner et al., 2016; Gispen-De Weid, 2000; Jones and Fernyhough, 2007; Walder et al., 2000; Walker and Diforio, 1997). Psychosis when occurring with depression in PMD is shown to be associated with greater cognitive impairments and higher cortisol compared to non-psychotic depression (Belanoff et al., 2001; Keller et al., 2006). Thus, schizophrenia patients with more positive symptoms have been associated with better cognition compared to those with negative symptoms though of higher levels of cortisol, which may be contradictory to the affective literature which finds psychotic depression associated with worse cognition and higher levels of cortisol.

In spite of large bodies of research examining cortisol or cognitive function in different psychiatric diagnoses, there remain an uncertain relationship among clinical symptoms (including depression and psychosis), cortisol, and cognitive function. This study attempts to clarify whether the relationship between hypercortisolemia and poor cognition in PMD is seen in patients with schizophrenia where psychosis and cognitive dysfunction are also hallmark features. Though we have previously reported on relationships of cortisol and cognition in PMDs and HCs (Keller et al., 2006; Keller et al., 2016), we have not explored the relationship of HPA axis, clinical symptoms, and cognition in SCZ patients nor have we made comparisons of SCZ to PMD patients.

2. Experimental materials and methods

2.1. Participants

Study participants were seen at Stanford University Medical Center in several studies of hypothalamic-pituitary-adrenal (HPA) activity in psychopathology (depression or schizophrenia). Forty-seven healthy controls (HC), 46 patients diagnosed with psychotic major depression (PMD), and 31 patients with schizophrenia spectrum disorders (8 with schizophrenia and 23 with schizoaffective disorder) participated. There were differences in education level with HCs having slightly higher education level than SCZ. Various subsets of the PMD and HC participants have been published previously (Keller et al., 2006; Gomez et al., 2006, and Keller et al., 2016). The SCZ data have not been previously published, with the exception of a small subsample of SCZ patients for the CVLT-II (Gill et al., 2018).

All participants were screened with the Structured Clinical Interview DSM-IV-TR Axis I Disorders (First et al., 1997), the 21-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Patients met DSM-IV criteria for their respective illness, either major depression with psychotic features, schizophrenia or schizoaffective disorder, or no history of any psychiatric illness. A total HAMD-21 score is used in data analyses. Several scores are created from the BPRS scale: BPRS total, BPRS positive symptom (PSS) subscale, and the negative symptoms subscale (NSS). The total score is simply the sum of the 18 BPRS items. The PSS consists of four items: conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. The NSS consists of three items: blunted affect, emotional withdrawal, and motor retardation. One point per item was backed out of the BPRS total, PSS, and NSS scales because the BPRS uses a 1 measure for the absence of symptomatology. This resets the scales to 0 equal to no symptoms.

PMD participants were required to have a baseline total score of 21 or higher on the HAMD-21 and a score of at least 7 on the Core Endogenomorphic Scale (Thase et al., 1983). PMDs had to score a minimum of 5 on the PSS scale. Schizoaffective disorder patients were required to have a HDRS-21 item total of 14 or more, and all SCZ patients were required to have a minimum score of 5 on the PSS scale. Healthy controls scored <6 on the HDRS-21 and had no psychotic symptoms as measured by the PSS. The healthy controls did not have a history of psychiatric disorders as determined by the SCID. Participants were allowed to remain on psychiatric

medications, if the dose had not been adjusted for at least one week. Participants who had ECT or Substance abuse in the last six months were excluded from the study. Patients were asked to refrain from caffeine use on the day of the study. None of the patients reported here were taking oral contraceptives or hormone replacement therapy because both increase circulating cortisol levels.

2.2. Neuropsychological measures by cognitive domains

Several cognitive domains were assessed, including Attention, Working Memory, Executive Functioning, and Verbal Memory and have been published previously, and full descriptions of the tests utilized can be found in Gomez et al., 2006.

In order to condense the cognitive testing, tests within a domain were forced into a single factor, via factor analysis. Tests were determined based on previous groupings of cognitive domains. There were four domains: Attention, Working Memory, Executive Functioning, and Verbal Memory. Attention consisted of the digit forward subtest from the WAIS-III and the Trail Making Test A. Working memory consisted of Digit Span Backwards and the Letter Number sequencing test from the WAIS-III. Executive Function consisted of Stroop Color Word test (color word condition), Trail Making Test B, and the Controlled Oral Word Association (FAS condition). Finally, Verbal Memory consisted on the CVLT-II short and long free recall conditions and the WMS III Logical Memory I and II. In addition, the total learning over the five learning trials from the CVLT-II was examined separately as a measure of learning.

2.3. Procedure

Study protocols received approval from the Stanford Institutional Review Board. Participants provided signed informed consent to participate in the study. They were admitted to the Stanford University Hospital General Clinical Research Center (G-CRC). Participants underwent psychiatric ratings and neuropsychological tests in the afternoon, and then underwent hourly blood sampling.

2.4. Cortisol sampling

Participants were admitted in the afternoon to the G-CRC, where they remained overnight. At 1600 h and blood was drawn every hour from 18:00 h to 09:00 h the following day from an extended intravenous line in order to assay cortisol levels. The blood sample was drawn from the extended line that permitted collection without entering the room or disturbing the participants, particularly important while they were sleeping. Participants were required to lie in bed 15 min prior to each blood sampling. Plasma was immediately separated from while blood by centrifuge and then stored at −20 °C before assay.

Cortisol assays were conducted by the Brigham Women's Hospital, General Clinical Research Laboratory in Boston. The analytic sensitivity for cortisol was 0.4 μg/dl with a coefficient of variation of <7.9%. Because of the natural diurnal rhythm of the cortisol slopes, the 15-hour blood collection period was divided into two phases based on the apparent nadir: the evening level from 1800 to 0100 h and the morning level from 0100 to 0900 h. These epochs correspond to the natural descending and ascending slopes of the cortisol rhythm and are based on the nadir observed in previous studies (11) of subsamples from this study. Cortisol means were then computed for these two epochs (1800 to 0100 and 0100 to 0900 h). Cortisol values were not normally distributed, so all cortisol values were log transformed. The transformed values were utilized in all data analyses.

2.5. Statistical analyses

All analyses were conducted using SPSS statistical software. First, ANOVA and Chi Square analyses were used to examine group differences in demographic variables (age, education, and gender), as well as clinical ratings (HDRS, BPRS). Next, ANCOVAs were utilized to examine differences in evening and early morning cortisol between the three groups, with age as a covariate because it is known to influence circulating cortisol levels (Lupien and McEwen, 1997; Van Cauter et al., 1996).

ANCOVAs were utilized to examine differences among the 3 diagnostic groups for each cognitive test. Finally, linear regression analyses were run predicting cognitive performance using subjects across all three groups. To avoid imposing our own bias, we ran a regression model that allowed the data to guide the outcomes, resulting in the most important predictors in the model to be detected. Thus, a forward regression approach was used for each dependent variable, and variable entry was set at 0.05 and variable removal was set at 0.10. The dependent variables were the cognitive factor scores. Independent variables included age, sex, depression severity, psychotic symptom severity, negative symptom severity, daily antipsychotic use, and log transformed mean evening cortisol (6 pm−1 am) and mean early morning cortisol (0100 h−0900 h).

Table 1
Demographics and clinical ratings of participants.

	PMD ($N=46$)	HC ($N=47$)	SCZ SP ($N=31$)	Analysis	Post-hoc comparison
Age	36.67 (12.4)	36.36 (12.5)	38.48 (12.6)	$F(2,121)=0.295$, ns $\eta_p^2=0.005$	
Education	15.04 (2.8)	15.69 (2.2)	14.26 (1.7)	$F(2,121)=3.59$, $p=.031$, $\eta_p^2=0.056$	HC=P, HC > S; P=S
WTAR predicted FIQ	$N=35$ 110.57 (10.5)	$N=42$ 111.31 (9.0)	$N=29$ 109.55 (9.8)	$F(2,103)=0.280$, ns $\eta_p^2=0.005$	
Gender				$\chi^2(2)=0.701$, ns	
Male	21	22	17		
Female	25	25	14		
Ethnicity				$\chi^2(8)=3.75$, ns	
Caucasian	32	39	12		
African Am	4	3	2		
Asian Am	6	12	1		
Latinx	2	4	1		
Other	1	1	0		
Daily psych medications^	Yes/No	Yes/No	Yes/N		
Any psych meds*	39/7	0/47	26/2	$\chi^2(1)=1.06$, ns	
Antidepressants	32/14		18/10	$\chi^2(1)=0.221$, ns	
Antipsychotics	28/17		23/5	$\chi^2(1)=3.25$, ns	
Anxiolytics/ Benzo	19/27		7/20	$\chi^2(1)=1.76$, ns	
Mood stabilizers	8/37		9/18	$\chi^2(1)=2.26$, ns	
HDRS	30.33 (5.4)	0.55 (0.9)	17.42 (9.1)	$F(2,121)=325.05$ $p<.001$, $\eta_p^2=0.843$	P > S > HC
BPRS total	48.04 (7.4)	18.55 (1.1)	37.17 (10.1)	$F(2,119)=228.1$ $p<.001$, $\eta_p^2=0.793$	P > S > HC
BPRS positive symptom subscale	12.04 (3.8)	4.06 (0.3)	10.24 (4.4)	$F(2,119)=80.32$ $p<.001$, $\eta_p^2=0.574$	P > S > HC
BPRS negative symptom subscale	8.76 (3.6)	3.09 (0.5)	5.93 (2.8)	$F(2,119)=54.22$ $p<.001$, $\eta_p^2=0.477$	P > S > HC

HDRS = Hamilton Depression Rating Scale; BPRS = Brief Psychiatric Rating Scale. Under Post-hoc comparisons, P = Psychotic Major Depression; HC = Healthy controls, S = schizophrenia spectrum disorders. This refers to the significance (p value) of the pairwise comparisons of the three groups. For example, under HDRS, PMD (P) subjects are significantly higher than SCZ (S) subjects, who score higher than HCs.
^Healthy controls not in the analyses.
* Any daily psychiatric medication includes use of antidepressants, antipsychotics, anxiolytics, or mood stabilizers.

The final model which was developed based on the forward regression, was set to an overall significance level $p \leq .005$. This was done to account for the large number of comparisons. Secondary analyses that examined the independent contributions of the chosen variables was set to alpha < 0.05.

3. Results

The 3 groups, PMD, HC, and SCZ, did not differ significantly with respect to age, gender, or ethnicity (see Table 1). Although the predicted intellectual functioning was similar across groups, the HC group had a slightly higher education level than the schizophrenia spectrum group. The majority of the patient groups were on medication, although there were no differences in the classes of medication they were taking. As expected, there were differences in ratings scales across groups. For all measures, HAMD total and BPRS total, PSS and NSS subscales the PMDs had higher scores than SCZs who had higher scores than the HCs (all p's < 0.001, see Table 1).

3.1. Cortisol

In examining the overnight cortisol graph, the PMD patients were observed to have higher cortisol in the evening, while SCZ subjects had lower cortisol in the early morning hours (see Fig. 1). With age as a covariate and using log transformed data, the three groups differed on mean evening (1800 h–0100 h) cortisol ($F(2,99) = 4.17$, $p = .018$; see Table 2). Interestingly PMD patients had higher mean evening cortisol compared to both SCZ ($p = .045$) and HC ($p = .009$), though HC and SCZ did not differ from each other ($p = .919$). Differences were also seen in early morning (0100 h–0900 h) cortisol among the 3 groups ($F(2,99) = 4.69$, $p < .011$).

SCZ patients had lower early morning cortisol than both PMD ($P = .009$) and HC ($p = .044$). Early morning cortisol did not differ between the HC and PMD groups ($p = .687$). Correlations between cortisol and clinical symptoms are shown in Table 3. With all three groups combined, there were statistically significant correlations between mean evening cortisol and negative symptoms, as well as depression severity.

3.2. Cognition

Overall, PMDs and SCZs had lower cognitive performance compared to the HC group. Both patient groups performed more poorly on measures of attention (Trail Making Test A), working memory (Digit Span Backward & Letter Number Sequencing), verbal memory (CLVT-II and Logical Memory), and executive functioning (Stroop Color Word, TMT B, COWA) than did HCs (see Table 2). In addition, both patient groups learned fewer words over the five learning trials on the CVLT-II compared to HC. Overall, PMDs and SCZs performed similarly to each other across all tasks.

Moderate correlations were demonstrated between cortisol and cognitive factors (see Table 3). In the overall sample, mean evening cortisol was significantly negatively correlated with the Verbal Memory ($r = -0.229$) and Executive Functioning ($r = -0.253$) factor scores, while the Attention factor was positively correlated with evening cortisol ($r = 0.250$). Similar correlations were found individually in the PMD and SCZ group for verbal memory and executive functions, though because of smaller sample sizes they did not necessarily reach statistical significance (see Table 3). The PMD group however has a significant correlation between Executive Function and evening cortisol ($r = -0.351$). Interestingly, in the SCZ group, the Working Memory factor was highly correlated with evening cortisol ($r = -0.628$). Early morning cortisol was also correlated with the Attention Factor, but in a negative manner ($r = -0.232$) in the overall sample. Though size and direction of the correlations were similar individually for the SCZ and PMD groups, they were not significant. In examining the relationship between positive and negative symptoms and depression, in the entire sample, negative symptoms were correlated with evening cortisol ($r = 0.326$), and this was also found with PMD patients alone ($r = 0.379$).

3.3. Linear regressions

Results of the Forward Linear Regression with the entire sample predicting cognitive performance are displayed in Table 4. Of the variables in the model, evening cortisol, age, and use of antipsychotic medication predicted verbal memory performance ($F(3,86) = 10.85$, $p < .001$, 27.5%). The use of antipsychotic medication accounted for the largest amount of variance (16.5%), followed by age (7.2), followed by evening cortisol (3.8%). Not using antipsychotics, older age, and lower cortisol were all associated with better verbal memory. On the verbal list learning tasks, depression severity and sex predicted overall learning ($F(2,87) = 14.48$, $p < .001$, 25.0%). Depression severity accounted for the largest proportion of variance (16.0%) followed by sex (9.0%).

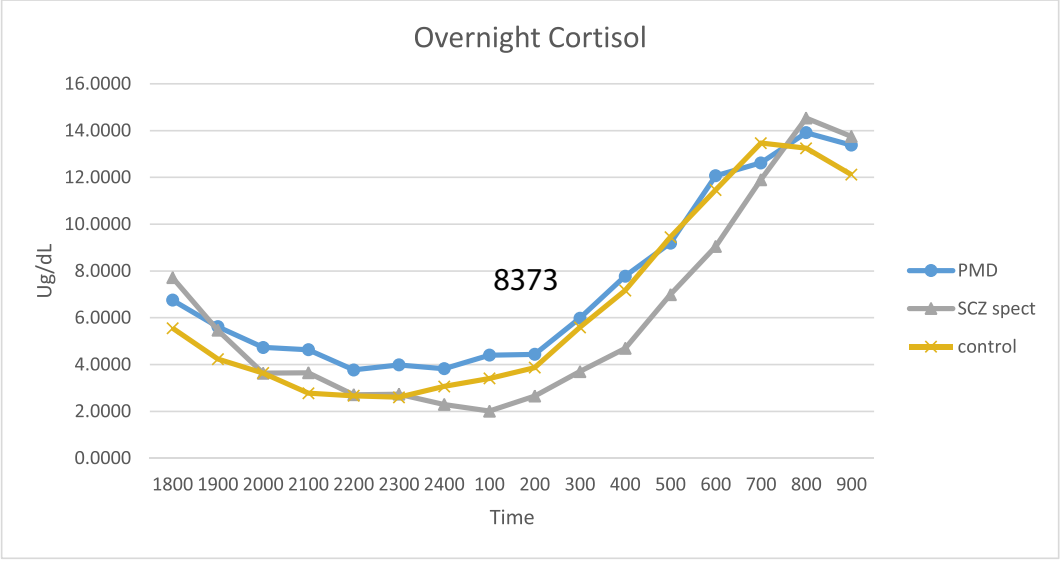

Fig. 1. Plots of overnight cortisol for the three groups from 1800 h to 0900 h.

Table 2
Results of Cortisol Levels and Neuropsychological Tests, includes Means (SD) and data analysis.

	PMD (N = 46)	HC (N = 47)	SAD (N = 31)	Analysis	Post-hoc comparisons
Cortisol*					
Mean cortisol 1800–0100	*N* = 43 4.82 (2.4)	*N* = 44 3.42 (1.3)	*N* = 16 3.77 (1.7)	F(2,99) = 4.17, *p* = .018 η_p^2=0.078	P > (H = S)
Mean CORTISOL 0100–0900	9.20 (4.0)	8.74 (2.2)	7.77 (3.1)	F(2,99) = 4.69, p = .01, η_p^2=0.086	(P = HC) > S
Attention					
Digit span forwards	*N* = 45 10.51 (2.9)	N = 42 11.26 (2.1)	N = 31 11.00 (4.1)	F(2,114) = 0.699, ns, η_p^2=0.012	
Trail making test A (time in seconds)	*N* = 41 32.68 (12.7)	N = 43 24.33 (8.8)	*N* = 28 33.46 (12.8)	F(2,108) = 8.08 *p* = .001, η_p^2 =0.130	(S=P) > HC
Working memory					
Digit span backwards	N = 45 6.80 (2.3)	N = 42 8.10 (2.5)	N = 31 6.81 (2.8)	F(2,114) = 3.57, p = .031, η_p^2=0.059	HC > (S=P)
Letter number sequencing	9.60 (2.8)	11.50 (3.0)	9.74 (2.8)	F(2,114) = 5.62 *p* = .005, η_p^2=0.090	HC > (S=P)
Executive function					
Stroop color-word (# items read)	N = 41 36.24(10.5)	N = 43 47.3 (13.0)	N = 28 37.12 (11.2)	F(2,108) = 12.33 p < .001, η_p^2=0.186	HC > (P=S)
Trail making test B (time/s)	78.03 (30.8)	60.99 (24.8)	95.41 (66.2)	F(2,108) = 5.93 *p* = .004, η_p^2 =0.099	(S=P) > HC (P=HC) *p* = .056
COWA (FAS)	37.07 (12.0)	45.05 (13.1)	37.86 (11.5)	F(2,108) = 5.11 *p* = .008, η_p^2=0.087	HC > (S=P)
Verbal memory					
CVLT-II	*N* = 40	N = 42	N = 29		
Total learning Trials 1–5	45.00 (12.4)	56.83 (9.2)	43.03 (12.9)	F(2,107) = 15.71 p < .001, η_p^2=0.227	HC > (P=S)
Short delay free	9.45 (3.6)	11.93 (2.7)	8.83 (3.9)	F(2,107) = 8.79 p < .001, η_p^2=0.141	HC > (P=S)
Long delay free	9.45 (4.0)	12.60 (2.8)	8.72 (3.8)	F(2,107) = 12.56 p < .001, η_p^2=0.190	HC > (P=S)
Logical memory					
Immediate recall	N = 44 21.86 (6.5)	N = 45 28.84 (8.3)	N = 31 21.13 (9.0)	F(2,116) = 12.14 p < .001, η_p^2=0.173	HC > (P=S)
Delayed recall	20.48 (8.3)	29.93 (6.8)	20.10 (12.0)	F(2,116) = 16.54, p < .001, η_p^2=0.222	HC > (P=S)

* Raw cortisol data is presented, but analyses used the log transformed cortisol values.

Interestingly, negative symptoms and age predicted executive function performance (F(2,90) = 9.82, p < .001, 17.9%). More negative symptoms and higher age were both associated with poorer executive function. Positive symptoms, sex, and age predicted attention (F(3,91) = 11.29, p < .001, 27.1%) performance. More positive symptoms, being female, and higher age all predicted worse attentional performance. Working memory was predicted by depression severity and sex ((F2,92) = 6.96, *p* = 002, 13.1%), with

Table 3
Partial correlations between cognitive measures and log transformed cortisol with the effects of age taken out, for the entire sample, including healthy controls, and then separately for each diagnostic group.

	HC Only		PMD only		Schizophrenia spectrum only	
	Evening cortisol	Early morning cortisol	Evening cortisol	Early morning cortisol	Evening cortisol	Early morning cortisol
Clinical ratings						
Positive symptom subscale	−0.117	−0.222	−0.039	0.063	−0.080	−0.421
Negative symptom subscale	0.142	0.124	0.379*	0.284	0.153	−0.213
HDRS depression	0.253	−0.197	0.125	−0.079	0.214	−0.266
Attention factor	0.346	0.070	0.229	−0.265	0.246	−0.329
Working memory factor	0.137	−0.130	−0.148	0.076	−0.628*	0.013
Executive function factor	−0.093	−0.027	−0.351*	0.237	−0.255	0.021
Verbal memory factor	0.034	−0.211	−0.252	−0.242	−0.381	−0.256

	Entire sample (PMD, HC, SCZ)	
	Evening cortisol	Early morning cortisol
Clinical ratings		
Positive symptom subscale	0.097	−0.196
Negative symptom subscale	0.326**	0.055
HDRS depression	0.217	−0.151
Attention factor	0.250*	−0.232*
Working memory factor	−0.153	0.083
Executive function factor	−0.253*	0.212
Verbal memory factor	−0.229*	0.021

**p < .01, *p < .05.

Table 4
Results of the Forward Regression Models predicting cognitive performance. Age, sex, depression severity, positive symptom severity, negative symptom severity, mean evening cortisol, mean early morning cortisol, and daily antipsychotic medication use were all potential predictors. Statistics for the full model are given, and the predictors that made it into the model are immediately below. Beta and t and *p* values once the other predictors are accounted for are provided. Entire sample includes PMD, HC, and SCZ.

Domain	Full model	Std. beta coefficient	t value	p value	% variance
Attention factor	$F(3,91) = 11.29$, $p < .001$, 27.1%				
	Positive symptoms	0.302	3.24	0.002	15.5
	Sex	0.263	2.84	0.006	5.7
	Age	0.246	2.72	0.008	5.9
	$F(2, 92) = 6.96$, $p = .002$, 13.1%				
Working memory factor	Ham 21 Total	−0.267	−2.72	0.008	9.0
	Sex	−0.207	−2.11	0.038	4.1
	$F(2,90) = 9.82$, $p < .001$, 17.9%				
Executive function factor	BPRS Negative Symptoms	−0.344	−3.58	0.001	13.6
	Age	−0.210	−2.19	0.031	4.3
	$F(3,86) = 10.85$, $p < .001$, 27.5%				
	Use of antipsychotics	−0.394	−4.28	<0.001	16.5
Verbal memory factor	Age	0.271	2.95	0.004	7.2
	Evening cortisol	−0.196	−2.13	0.036	3.8
	$F(2,87) = 14.48$, $p < .001$, 25.0%				
CVLT raw total (learning)	Ham 21 Total	−0.422	−4.53	<0.001	16.0
	Sex	0.300	3.22	0.002	9.0

Note: Attention Factor is the Trail Making Test − Subtest A and Digit Span Forward from the Wechsler Adult Intelligence Scale-III (WAIS-III); Working Memory Factor is the Digit Span Backwards from the WAIS −III; Letter Number Sequencing from the WAIS-III; Executive Functions Factor is the Trail Making Test − Subtest B; Stroop Color Word − Color Word reading; Controlled Oral Word Association Test using the letters F, A, S; Verbal Memory Factor is the Logical Memory Subtest of the Wechsler Memory Scale-III; and the California Verbal Learning Test 2nd Edition (CVLT); CVLT Raw Total was indicated separately as a measure of verbal learning.

more depression and being female predicting worse working memory performance.

4. Discussion

Data presented indicate that PMDs have higher evening basal cortisol compared to HC and SCZ patients. SCZ patients did not differ from HCs. Our findings suggest that ambient evening cortisol functioning is not as dysregulated in the SCZ population in comparison to PMD, where it is markedly elevated in the evening. The results of this study demonstrate increased HPA activity in psychosis in the presence of a primary mood disorder but not in SCZ.

Age and negative symptoms were the primary predictors of cortisol levels. This finding is contrary to several studies in schizophrenia that have found positive symptoms correlating with higher cortisol (Coulon et al., 2016; Garner et al., 2016; Gispen-De Weid, 2000; Jones and Fernyhough, 2007; Walder et al., 2000; Walker and Diforio, 1997), although not all reports agree (Chaumette et al., 2016). There is much variability in the SCZ literature and most studies have focused on cortisol in response to stressors rather than as a cross-sectional baseline.

With respect to cognitive performance, PMD and SCZ patients performed similarly, demonstrating impaired performance across multiple domains including attention, working memory, executive functioning, and verbal learning and memory. Both patient groups performed more poorly than HC. Previous work demonstrated that PMD patients perform worse cognitively than depressed patients without psychosis (Gomez et al., 2006; Gomez et al., 2009), suggesting that the reduced cognitive performance in PMDs is likely related to the addition of psychotic features to depression. SCZ patients were less acutely ill or more fully treated than were the PMDs as suggested by PMDs greater clinical symptomatology. PMDs actually presented with a greater degree of both positive and negative symptoms, as well as those of depression, than did SCZ patients, suggesting that our findings are not just a function of severity of illness, as SCZ performed similarly to PMDs on cognitive measures despite their relatively intact evening basal cortisol.

Clinical symptoms and cortisol were both contributors to cognition in the present study. However, despite strong and consistent negative relationships between cognitive factors and mean evening cortisol in the present study, regression analyses suggest that clinical symptoms were stronger predictors of poor cognition than was cortisol in the overall group of PMD and SCZ. Attention was most strongly influenced by the presence of positive symptoms, while executive function was most influenced by the presence of negative symptoms. Furthermore Depression appeared to contribute most strongly to difficulties with verbal learning and working memory, which is interesting given the very strong correlation ($r = -0.628$) found specifically between working memory and evening cortisol within the SCZ group. Evening cortisol only influenced verbal memory. Basso et al. (1998) found that the presence of positive symptoms was not associated with neuropsychological impairment, which is consistent with these data that point to a direct effect of clinical symptoms on cognitive function that is independent of cortisol. Clinical symptoms accounted for between 9 and 16% of the variance of a variety of cognitive variables (Attention, Working Memory, Executive Functions, Verbal Learning), while cortisol accounted for approximately 4% of the variance of verbal memory only.

These findings likely reflect that patients diagnosed with schizophrenia in this study were generally less acutely ill which may account for their normal diurnal rhythm and mean cortisol levels. Research suggests that the increase in cortisol secretion takes place before an acute episode and seems therefore to be an indicator of the vulnerability to schizophrenia (Walker et al., 2010, Karanikas and Garyfallos, 2015; for review see Coulon et al., 2016). Thus, in SCZ increased cortisol may be a better marker of the phase of illness. Indeed, Walker and Diforio (1997) described the hippocampus and HPA axis as the mediating pathway between environmental stressors, underlying vulnerability and development of the disorder, and this model has been extended by involving genetic predictors (Van Winkel et al., 2008), as well as inflammation and microglia (Howes and McCutcheon, 2017). Excessive neuronal pruning in stress-sensitive areas could account for the development of negative symptoms and cognitive inefficiency in schizophrenia (Shepherd et al., 2012). It is possible that a similar stress vulnerability mechanism related to immune function is at work in patients with psychotic major depression (Rohler et al., 2010) and thus, the elevation in cortisol and cognitive deficits seen in PMD represents this same vulnerability to psychosis, rather than the psychosis itself per se. Follow up data with patients once they have remitted from the acute depression with psychotic features may provide clarity on whether a similar stress vulnerability is seen in PMD.

4.1. Limitations and future research

The present study has several limitations. Although we surveyed cortisol activity hourly for 15 h and included all night sampling, the sample sizes for overnight cortisol in the SCZ was smaller than for the other 2 groups. In order to address small sample sizes, we combined patients with schizoaffective disorder with patients with schizophrenia to form the schizophrenia spectrum group. This combination may have a confounding effect on the results. Larger sample sizes would be required to confirm and extend on these results. The smaller sample size also influences our choice of

statistical analyses and confounds the large number of analyses conducted. Numerous analyses increase the risk of committing a Type I error and as such the threshold for which analyses were considered significant was tightened to address this issue. At any rate, these findings are in need of larger samples for replication.

Another potential confounding issue is that of medication. There are complex relationships between medication and cortisol, including effects of sex and genotypes (Klok et al., 2011). The rate of medication use across classes of medication did not differ between our study samples with the exception of antipsychotic use. There is some evidence that antipsychotic medications affect cortisol expression (Walker et al., 2008). Only two patients were taking typical antipsychotics, which the remaining participants on antipsychotic medications were taking atypical agents. Thus, there were not sufficiently large samples to examine for potential differences related to antipsychotic type. To the extent possible, use of antipsychotic medication was taken into consideration as a binary variable as to whether patients were taking antipsychotic medication daily or not.

The use of nicotine was not collected. This may be another confounding issue as nicotine is understood to be associated with elevations in cortisol across the diurnal pattern (Steptoe and Ussher, 2006). Furthermore, nicotine cessation is shown to be associated with HPA abnormalities and impaired cortisol stress response (Gilbert et al., 2000; Lovallo, 2006).

Review of the body of literature on cortisol reveals great heterogeneity in cortisol sampling procedures. Different sampling methodologies can both influence cortisol expression as well as measure different aspects of HPA activity and cortisol, for example, salivary cortisol is understood to represent acute stress reactivity, while hair sampling provides a measure of long-term cortisol secretion. Blood draw, used in the current study, provides a measure of circulating cortisol. Although serum cortisol can also be estimated by salivary methods (Duplessis et al., 2010), as there were overnight hourly samples taken, blood draw was determined to be the least disturbing to the study participants, and therefore the least likely method of cortisol sampling to have an impact on cortisol levels themselves.

There is very limited research specifically examining HPA axis function and cognition in schizophrenia and PMD. The diathesis stress model of symptom expression is prominent for both of these disorders and research often points to interactions, particularly with environment, stress, and genetics. Although separate models have been developed and studies run, a collaborative examination to understand the overlapping psychotic and affective symptoms may add a dimension of understanding to their individual models. Studies that examine the commonalities across these disorders, including genetics, environment, stress, and trauma, along with the extensive data from the present study (cognition, symptom ratings, cortisol) are lacking. Consequently, forward regression analyses were examined. Comprehensive examination on larger, independent samples is needed to confirm the present findings and to extend upon them to more fully understand the inherently complex interactions of genes and environment in the expression of mood and psychotic symptoms.

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Contributors

Alan Schatzberg designed the study and wrote the protocol. Jennifer Keller helped design the protocol, oversaw implementation of the study, and undertook statistical analysis. Kirsten Cherian managed the literature reviews and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

Although there is not a conflict of interest, there may appear to be one with Dr. Schatzberg. He has a significant interest in Corcept Therapeutics, Inc., which licensed the use patent for mifepristone in psychotic major depression. Some of the data presented here were part of a larger study examining the effectiveness of mifepristone in psychotic major depression, as well as a larger study examining the effectiveness of mifepristone in schizophrenia. No data on mifepristone's effectiveness are presented in the submitted report.

Dr. Keller has no reported conflicts of interest.

Kirsten Cherian has no reported conflicts of interest.

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