Cognitive Functioning, Cortisol Release, and Symptom Severity in Patients with Schizophrenia

Deborah J. Walder, Elaine F. Walker, and Richard J. Lewine

Background: *There is substantial evidence of dysregulation of cortisol secretion, hippocampal abnormalities, and memory deficits in schizophrenia and other psychotic disorders. Research also suggests that cortisol secretion augments dopaminergic activity, which may result in increased symptom expression in this clinical population.*

Methods: *We examined the relations among cortisol release, cognitive performance, and psychotic symptomatology. Subjects were 18 adults with schizophrenia or schizoaffective disorder, seven with a nonpsychotic psychiatric disorder, and 15 normal control subjects. Tests of memory and executive function were administered. Cortisol was assayed from multiple saliva samples.*

Results: *Findings indicated the following: 1) patients with psychotic disorders scored below the comparison groups on the cognitive measures; 2) for the entire sample, cortisol levels were inversely correlated with performance on memory and frontal tasks; and 3) among patients, cortisol levels were positively correlated with ratings of positive, disorganized, and overall symptom severity, but not with negative symptoms.*

Conclusions: *The present results suggest that abnormalities in the hypothalamic–pituitary–adrenal axis and hippocampal systems play a role in observed cognitive deficits across populations. Among psychotic patients, elevated cortisol secretion is linked with greater symptom severity.* Biol Psychiatry 2000;48:1121–1132 © *2000 Society of Biological Psychiatry*

Key Words: Cortisol, hippocampus, memory, cognitive, symptoms, schizophrenia

Introduction

Patients with psychotic disorders manifest deficits in short-term verbal and visuospatial memory functions (Gold et al 1992a, 1992b; Goldberg et al 1990; Hoff et al 1992; Saykin et al 1994; Schmand et al 1992). Paralleling these findings, research has shown that schizophrenia is associated with hippocampal volumetric reductions (e.g., Bogerts et al 1985; Breier et al 1992; Jeste and Lohr 1989; Suddath et al 1990; Waldo et al 1994) and cellular abnormalities (e.g., Akbarian et al 1993; Altshuler et al 1990; Benes et al 1991; Bogerts et al 1990; Jeste and Lohr 1989; Kovelman and Scheibel 1984). In recent studies, reductions in hippocampal volume have been found in first-episode schizophrenia patients, suggesting that the abnormality is not a treatment artifact (Hirayasu et al 1998; Velakoulis et al 1999). This also extends to patients with other psychotic disorders (Velakoulis et al 1999).

A link between hippocampal morphology and memory has been established in studies of nonschizophrenic samples, such that the volume of the hippocampus is inversely related with memory test performance (Lencz et al 1992; Starkman et al 1992). This is consistent with the prevailing theory that the hippocampal system plays a major role in declarative (or explicit) memory (Eichenbaum et al 1996; Squire 1987, 1992). A few studies show no significant relationship between delayed memory and hippocampal volume in schizophrenia spectrum patients (Colombo et al 1993; Delisi et al 1991; Nestor et al 1993; Torres et al 1997). In contrast, Goldberg et al (1994) found a strong association between intrapair differences in a parameter of verbal memory and intrapair differences in left hippocampal volume in monozygotic twins discordant for schizophrenia. Discrepancies in these findings may be due to variability in the cognitive measures selected to index memory. It is also noteworthy that Goldberg et al (1994) focused on the hippocampal volume difference between affected twins and their healthy monozygotic cotwins. Thus, there was some control for genetically determined differences in volume.

In addition to its role in memory functioning, the hippocampus is assumed to play a role in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis. Specifically, it appears that the stimulation of glucocorticoid receptors in the hippocampus contributes to a negative feedback system that dampens HPA activity. Animal studies suggest that prolonged stress and elevations in corticosteroids can damage the hippocampus (Sapolsky and McEwen 1986; Sapolsky et al 1990), which may lead to dysregulation of the HPA axis via a decrease in glucocorticoid negative feedback. Thus, studies of human subjects revealing an inverse correlation between cortisol

From the Departments of Psychology (DJW, EFW) and Psychiatry (RJW), Emory University, Atlanta, Georgia.
Address reprint requests to Deborah J. Walder, M.A., Emory University, Department of Psychology, 532 North Kilgo Circle, Atlanta GA 30322.
Received March 28, 2000; revised August 28, 2000; accepted September 1, 2000.

0006-3223/00/$20.00
PII S0006-3223(00)01052-0

and hippocampal volume (Rao et al 1989; Starkman et al 1992) are not surprising.

Consistent with the above findings, there is also an inverse relation between cortisol level and performance on measures of hippocampal function, particularly declarative memory, in healthy human subjects. This relation has been shown in experimental studies in which glucocorticoids are manipulated and memory decrements ensue (Kirschbaum et al 1996; Newcomer et al 1994, 1999), studies in which stress-induced alterations in cortisol are associated with memory deficits (Lupien et al 1997), and longitudinal studies of the relation between age-related declines in cortisol and memory performance (Seeman et al 1997). It is noteworthy that Kirschbaum et al (1996) showed that memory performance deficits follow acute, relatively low-stress exposure (e.g., Trier Social Stress Test), or what is presumed to be relatively low-dose increases in cortisol. In contrast, one more recent study (Newcomer et al 1999) found that similar cognitive impairments following exogenous glucocorticoid treatment are high-dose specific (e.g., approximating cortisol exposure during moderate to maximum stress conditions). Future research aimed at clarifying the specific effects of low- versus high-dose and acute versus chronic glucocorticoid exposure is warranted.

The precise nature of memory deficits following acute elevations in cortisol is also unclear. Some studies suggest impairments in immediate recall following stress-induced cortisol secretion (Lupien et al 1997), whereas others suggest a retrieval-specific impairment following exogenous administration of corticosteroids (De Quervain et al 2000). Overall, this body of literature suggests that cortisol is linked with memory function in two ways: 1) directly, by acutely disrupting working memory and short-term recall, and 2) indirectly, through the effects of persistent cortisol elevations on hippocampal integrity.

To date, only two studies have explored the relation between glucocorticoids and memory performance in schizophrenia. One early report (Newcomer et al 1991) showed an inverse relation between early morning (8:00 AM) postdexamethasone cortisol levels and auditory verbal learning deficits in unmedicated schizophrenic patients. In a more recent experimental study, Newcomer et al (1998) examined the effects of dexamethasone versus a placebo on verbal memory performance in schizophrenic patients over 4 days. The finding of an association between higher plasma cortisol concentrations (before dexamethasone treatment) and reduced memory performance in patients with schizophrenia extended their earlier findings. There was no relation, however, between postdexamethasone cortisol levels and recall performance. It is noteworthy that although several studies evidence elevated basal levels of cortisol (Walker and Diforio 1997) and postdexamethasone nonsuppression (Arana et al 1983; Sharma et al 1988) in schizophrenia, these findings are not consistently observed in this population.

Previous studies indicate a relation between HPA activity and symptomatology in schizophrenia. In some, cortisol secretion was primarily associated with more severe positive symptoms (Kaneko et al 1992; Keshavan et al 1989; Rybakowski et al 1991), whereas in others it was associated with higher ratings of negative symptoms (Newcomer et al 1991; Tandon et al 1991). It has been suggested that the relation between cortisol levels and symptom severity is due to the augmenting effects of cortisol on dopamine activity (Walker and Diforio 1997).

Findings from several studies revealing a relation of pre- or postdexamethasone suppression test cortisol levels with psychotic symptoms suggest that this association is not affected by level of depression (Schatzberg and Rothschild 1988; Sharma et al 1988). Thus, the association of cortisol with symptom severity is not attributable to the presence of mood disorder in some psychotic patients.

This study is based on the assumption that heightened cortisol release is associated with memory deficits in normal healthy control subjects. Thus, it was hypothesized that cortisol level would be inversely correlated with memory performance in patients with psychotic disorders. In addition, we examined the association of symptom severity with both cortisol secretion and memory performance. Given the evidence that HPA activation augments dopamine activity (Schatzberg et al 1985), it was predicted that elevated cortisol levels would be associated with increased symptom severity. This study is novel in that it examines the relations among cognitive performance, symptom expression, and neuroendocrine measures in a psychiatric population, in the absence of the stress typically associated with blood sampling procedures or exogenously administered pharmacologic agents.

To better understand the association of the HPA axis with memory and symptom expression, cortisol levels were assessed at multiple time points. It is important to note that participation in a research study may, in itself, constitute a psychological stressor for many individuals (Weinstein et al 1999). At the very least, the research laboratory is a novel context for most people. This, in turn, may influence tonic measures of cortisol. Thus, what is often conceived of as "baseline" cortisol (e.g., the initial cortisol sample upon entry into a study) may not be a true index of stable cortisol levels for the individual. Instead, this initial measure of cortisol may be an index of sensitivity to novelty and reflective of HPA stress responsivity. In contrast, cortisol levels sampled after the individual is acclimated to the research setting may better approximate baseline levels of cortisol and serve as an index of hippocampal integrity, as the novelty of the

Table 1. Characteristics of Current Sample

	Psychotic disorders (1)	Other disorders (2)	Normal control subjects (3)	Grand total	Difference between groups
Number of subjects					
Total	18	7	15	40	
Male	10	3	6	19	
Female	8	4	9	21	
Age (years)					
Mean (SD)	36.72 (11.66)	26.71 (3.95)	25.67 (8.18)	30.83 (10.72)	$2 < 1$,[a] $3 < 1$[b]
Race					
White	11	4	9	24	
African American	7	2	2	11	
Asian–Pacific	0	1	2	3	
Missing data	0	0	2	2	

[a] $p < .05$, one-tailed test.
[b] $p < .01$, one-tailed test.

situation diminishes. These factors were considered when interpreting the findings in this study.

Methods and Materials

Subjects

The study samples were 15 normal control (NC) subjects, 18 patients with current or past (in remission) diagnosis of a psychotic disorder (PD), and seven individuals with other psychiatric disorders (ODs). Subjects ranged from 18 to 58 years of age, with an overall mean age of 30.8 years (see Table 1 for demographic characteristics). The PD group included patients who met DSM-IV criteria for schizophrenia, including paranoid, disorganized, residual, and undifferentiated type ($n = 12$) or schizoaffective disorder ($n = 6$). Subjects in the OD group met criteria for affective disorders without psychotic features (e.g., major depressive disorder, history of a major depressive episode), and one subject met criteria for pervasive developmental disorder. Normal control subjects were recruited from the community; all other subjects were recruited from inpatient and outpatient psychiatric services. Fifteen of the 18 subjects with psychotic disorders were being treated with antipsychotics. Some patients refused medication.

Informed consent was obtained from all subjects before their participation in this research study. The study protocol was reviewed and approved by the Human Investigations Committee at Emory University before data collection.

Diagnostic Instruments

DIAGNOSTIC INTERVIEW. The Structured Clinical Interview for DSM-IV, research version (SCID-IV; First et al 1997), the Schedule for Assessment of Positive Symptoms (SAPS; Andreasen 1983), and the Schedule for Assessment of Negative Symptoms (SANS; Andreasen 1981) were administered by trained examiners to all participants at the initial assessment. Diagnostic interviews were videotaped so that consensus diagnoses could be established.

SALIVA SAMPLING FOR THE ASSAY OF CORTISOL. The measurement of salivary cortisol has been purported to be a reliable tool for investigating HPA activity (Kiess et al 1995; Kirschbaum and Hellhammer 1989; Laudat et al 1988). Moreover, as pointed out by Weinstein et al (1999), salivary, urinary, and plasma measures of cortisol are highly interrelated, as well as comparable in sensitivity as measures of stress reactivity (Bassett et al 1987; Shipley et al 1992). Finally, the noninvasive nature of saliva sampling yields it a more preferable method for repeated assessments (Baum and Grunberg 1995).

Saliva samples (about 1 mL each) for the assay of cortisol were obtained from subjects three to five times during the assessment. These samples were obtained by asking the subjects to spew saliva into plastic specimen tubes, in which the samples were stored. To maintain uniformity in the portion of the diurnal variation in cortisol excretion represented in the samples, all assessments were conducted at the same time of day. The first sample was obtained at approximately 8:00 AM. Subsequent samples were obtained at approximately 9:00 AM, 10:00 AM, 11:00 AM, and 12:00 PM. By obtaining multiple measures, it was possible to examine group and individual differences in change, as well as mean levels.

CORTISOL ASSAY. The saliva samples were prepared for assay according to standard procedures. They were stored at −20°C in a 13–cu ft S/P (Asheville, NC) cryofreezer. In preparation for assay, the samples were rapidly thawed and centrifuged at 300 *g* for 10 min to remove coagulated protein and other insoluble material. Cortisol was assayed in duplicated 200-μL aliquots of the clear supernatant using materials and procedures provided by Incstar (Stillwater, MN). The assay was performed in tubes coated with an antiserum that shows significant cross-reactivity only with prednisone (83%), 11-deoxycortisol (6.4%), cortisone (3.6%), and corticosterone (2.3%). Standards in the range 1–30 ng/mL consisted of the serum standards provided with the kit materials diluted with 200 μL of phosphate-buffered saline. Protein concentrations were equalized in standards and samples by adding cortisol-free serum to the

samples. For the most recent assays conducted by the lab, the mean coefficients of variation between duplicates and between assays were less than 5%. Relative to the serum standards, the mean recovery of cortisol from saliva has been indistinguishable from 100%.

Neuropsychological Assessment

The neuropsychological measures were selected to yield a comprehensive profile of hippocampal functioning and attentional functioning.

HIPPOCAMPAL FUNCTIONING. *California Verbal Learning Test (CVLT; Delis et al 1983)* The CVLT is typically used to assess memory deficits associated with hippocampal functioning. It measures recall and recognition of lists containing related words, across several trials.

The composite score derived for this test was an average of the standardized scores on the seven subtests of this measure, including two measures of immediate recall, two measures of short-delay recall (free and cued), two measures of long-delay recall (free and cued), and one measure of long-delay recognition. Higher scores indicate better performance.

Wechsler Memory Scale—Revised (WMS-R; Wechsler 1987) Subtests of the WMS-R are also frequently used to assess memory deficits associated with hippocampal functioning. The WMS-R scales require recall of stories and paired word associates. Patients with schizophrenia have significant memory impairments on the original Wechsler Memory Scale (Goldberg et al 1990) and the WMS-R (Gold et al 1992b). Research findings suggest that memory impairment based on this measure is not solely attributable to general cognitive deterioration in schizophrenia (Gold et al 1992b). The four subtests administered from this measure (Logical Memory I, Logical Memory II, Verbal Paired Associates I, and Verbal Paired Associates II) focus on short-term learning, recall, and delayed recall of verbal material.

The composite score derived for the WMS-R was an average of the standardized scores on the four subtests, immediate and delayed recall of a story, and immediate and delayed recall of verbal paired associates. Higher scores indicate better performance.

Modified Wisconsin Card Sorting Test (MCST; Nelson 1976) This test is a simplified version of the Wisconsin Card Sorting Task, revised to reduce ambiguity concerning the sorting principle active at any point in the test. Poor performance on the MCST has been demonstrated in schizophrenic patients (Nelson 1976). The MCST is a measure traditionally used to assess frontal lobe (or executive) functioning. There is evidence, however, suggesting that volume reductions in the anterior hippocampal formation may predict neuropsychological deficits in executive functions (Bilder et al 1995). Therefore, given the hypothesized connectivity between the frontal and hippocampal brain regions, the MCST was selected as an additional potential indicator of hippocampal-related deficits.

In this test the subject is required to sort a deck of stimulus cards into groups corresponding to the color, form, or number printed on four key cards before him or her. The subject is not told the correct sorting principle but is informed by the examiner whether or not each card was sorted correctly. The subject must deduce the correct sorting rule based upon the information provided.

Indices derived from this test are total number of correct responses, total number of errors, and number of perseverative errors. The composite score was an average of the standardized scores for the total number of errors and number of perseverative errors. Thus, for total number of correct responses, higher scores indicate better performance. For the composite score, however, higher scores indicate poorer performance.

ATTENTION. *Continuous Performance Task—Vigil (CPT-Vigil) (ForThought, Nashua NH)* CPT-Vigil is a computerized attention measure typically used to assess vigilance, or maintenance of attention, over time. It has been shown to be a valid test of individual differences in vigilance performance (Buchsbaum and Sostek 1980). Because memory involves aspects of attention, this measure was administered to a subgroup of 33 subjects to examine the relation between memory performance and attentional functioning. Data were not collected on the remaining seven subjects of the total sample because of technical problems with computer equipment.

This computerized task measures sustained concentration and attention by presenting target stimuli (e.g., letters) on the computer screen one at a time. The "AK" version of the task, which requires the subject to press the space bar on the keyboard in response to a complex target stimulus (e.g., the letter *K* only when preceded by the letter *A*), was used. This stimulus is presented among other randomly presented nontarget stimuli (e.g., other letters of the alphabet presented in an order not ascribing to the rule outlined above).

The test apparatus consisted of a desktop computer monitor and keyboard. The signal stimuli were presented on the computer screen for a duration of 85.3 msec and at an interstimulus interval of 910.3 msec. A total of 100 targets out of 480 total stimuli were presented. The stimulus sequence was randomized. A response to a nontarget stimulus was considered an "error of commission," and a failure to respond in the presence of a target stimulus was considered an "error of omission." From these measures, an index of sensitivity (d') was derived and used in the current analyses. Sensivity (d') has been shown to have moderate reliability (Buchsbaum and Sostek 1980) and is a measure of attentiveness or discriminability.

Procedures and Time Frame

The order of administration of the tests was the same for all subjects: CVLT (immediate recall), MCST, CVLT (20-min delayed recall), subtests of the WMS-R (immediate recall), subtests of the WMS-R (delayed recall), and CPT-Vigil.

Assessments began at approximately 8:00 AM, with a description of the study goals and measures, and took roughly 3.5–4.5 hours to complete. The consent form described the procedures for maintaining confidentiality, the study protocol, and the subject's right to withdraw from participation at any time.

The first saliva sampling was at 8:00 AM, followed by one

Table 2. Correlation Coefficients for Cortisol Measures for Total Sample

	Index				
	Cortisol at time 1	Cortisol at time 2	Cortisol at time 3	Mean cortisol	Slope of cortisol
Cortisol at time 1	—	—	—	—	—
Cortisol at time 2	.460[a]	—	—	—	—
Cortisol at time 3	.251	.657[a]	—	—	—
Mean cortisol	.800[a]	.867[a]	.702[a]	—	—
Slope of cortisol	.622[a]	.911[a]	.844[a]	.965[a]	—

[a] $p < .01$, one-tailed test, $n = 40$.

every hour. The diagnostic interview (SCID-IV), from which SANS and SAPS ratings were determined, followed the initial saliva sampling and was followed by the neuropsychological assessment. All interviewers were trained in conducting the SCID-IV before commencement of this study. The neuropsychological assessment was administered by another trained research assistant, who was blind to the subjects' interview results.

Subjects were asked to refrain from alcoholic beverages for one day before the assessment. They were also instructed to avoid consumption of caffeinated food and beverages beginning the night before the assessment and to eat a light breakfast before their appointment. Any deviations from the instructions were recorded.

Analysis

CORTISOL. Cortisol levels were measured at times 1, 2, and 3 for all subjects. Cortisol levels at times 4 and 5 were only collected for those subjects for whom the duration of the assessment continued for 3–4 hours. This was more often the case for subjects belonging to the inpatient and outpatient clinical samples, as compared with NC subjects. Because 42.5% of the total sample was missing data for cortisol at time 4 and 82.5% of the total sample was missing data for cortisol at time 5, these measures were excluded from all analyses.

Two additional indices of HPA activity were computed for each subject: 1) the average of cortisol at times 1, 2, and 3 and 2) the slope of cortisol across times 1, 2, and 3 (i.e., the linear slope of the regression of cortisol on time). The linear slope provides an index of the magnitude of the change in cortisol levels during the assessment period for each subject. The slope of cortisol has previously been used as a sensitive measure to index cortisol responsivity to the initial novelty of similar assessment procedures (Weinstein et al 1999). One-sample *t* tests were conducted comparing the slope for each of the four groups to a test value of zero. Results indicated that the slope value for each of the four groups was significantly different from zero (total sample, $t(39) = 14.143$, $p = .000$; NC group, $t(14) = 7.421$, $p = .000$; PD group, $t(17) = 9.296$, $p = .000$; OD group, $t(6) = 9.906$, $p = .000$).

Table 2 lists correlation coefficients among measures of cortisol. The high intercorrelations indicate reliable assay of cortisol levels.

It has been shown that exposure to novelty can heighten cortisol levels (Al'Absi and Lovallo 1993; Hennessy et al 1995). Thus, it is possible that in this study cortisol at time 1 served as an index of sensitivity to the initial novelty of the assessment. In contrast, saliva samples at times 2 and 3 may reflect baseline levels of cortisol. If this is the case, then the slope of cortisol may be an alternative measure of stress sensitivity as well, given that it indexes the magnitude of the linear change in cortisol from the initial level over time.

COGNITIVE MEASURES. Interitem correlations among the WMS-R, CVLT, and MCST standardized scores were examined and internal consistency (α) was computed. Results indicated high internal consistency among the four WMS-R subtests ($\alpha = .8804$), the seven CVLT subtests ($\alpha = .9445$), and the two MCST indices ($\alpha = .9424$). Therefore, *z* scores for the subtests of each of these measures were averaged together to derive CVLT, WMS-R, and MCST composite scores, respectively. Sensitivity (d') was calculated according to standard procedures (McNicol and Willson 1971).

The CVLT and WMS-R composite scores were highly correlated ($\alpha = .8516$). Therefore, they were averaged to compute an index of "explicit memory." There were high intercorrelations among the CVLT, WMS-R, and MCST total number of correct responses scores ($\alpha = .7947$). Therefore, the three scores were averaged to compute an aggregate index of "hippocampal functioning." Scaling was the same for all variables in the composite scores.

SYMPTOM RATINGS. Recent research findings suggest that a three-symptom dimension model may best fit the data on clinical symptoms in patients with schizophrenia (Andreasen et al 1995). Accordingly, positive symptoms are divided into two dimensions, a psychosis dimension (i.e., delusions and hallucinations) and a disorganized dimension (i.e., disorganized speech, disorganized behavior and inappropriate affect). The third dimension is composed of negative symptoms (i.e., affective flattening, physical anergia). Using Andreasen et al's (1995) three-factor solution, we derived Positive, Negative, and Disorganized Symptoms scale scores to measure symptomatology.

Internal consistency (Chronbach's α) was examined for each of the hypothesized scales, excluding items with missing data and/or that had restricted variance across ratings. The reliabilities for the hypothesized Positive Symptoms scale ($\alpha = .8631$), Negative Symptoms scale ($\alpha = .6986$), and Disorganized Symptoms scale ($\alpha = .7100$) were high. Therefore, ratings on the items within each scale were averaged to obtain a composite index of severity of positive, negative, and disorganized symptoms, respectively. The items comprising each scale and their associated criteria are contained in Appendix 1.

Neuropsychological dysfunction in schizophrenia may be more closely associated with overall symptom severity than specific symptom dimensions (Goldberg and Weinberger 1995). Therefore, ratings across the three symptom scales were averaged to create a global index of symptom severity. The reliability

Table 3. Correlation Coefficients and Partial Correlation Coefficients Relating Cortisol with Explicit Memory and Hippocampal Functioning, for Total Sample

	Index				
	Cortisol at time 1	Cortisol at time 2	Cortisol at time 3	Mean cortisol	Cortisol slope
Explicit memory[a] (no covariate)	.179	−.252	−.348[b]	−.114	−.228
Explicit memory[c] (with CPT sensitivity as covariate)	.121	−.342[b]	−.373[b]	−.192	−.301[b]
Hippocampal functioning[a] (no covariate)	.140	−.268[b]	−.316[b]	−.133	−.233
Hippocampal functioning[c] (with CPT sensitivity as covariate)	.052	−.449[d]	−.386[b]	−.279	−.379[b]
MCST[a]	−.074	.225	.189	.113	.173
MCST[c] (with CPT sensitivity as covariate)	.076	.489[d]	.248	.325[b]	.372[b]

CPT, Continuous Performance Test; MCST, Modified Wisconsin Card Sorting Test.
[a] $n = 40$.
[b] $p < .05$, one-tailed test.
[c] $n = 33$.
[d] $p < .01$, one-tailed test.

for this scale was low ($\alpha = .3078$). This was expected, given that the three scales were presumed to measure different dimensions of symptomatology.

DIAGNOSTIC GROUP DIFFERENCES. Independent-samples *t* tests were employed to test for group differences in age, cognitive performance, cortisol levels, and symptom scale ratings. One-tailed tests were used because the hypothesized group differences in the examined variables were directional in nature.

Group Demographics The PD group was significantly older than the OD group [$t(23) = 2.198$, $p = .019$] and NC group [$t(31) = -0.3090$, $p = .002$] (Table 1). χ^2 tests comparing the PD, OD, and NC groups on gender and race indicated no group differences in these demographic characteristics.

Cognitive Measures The PD group scored below the OD group on d' [$t(9) = -1.885$, $p = .038$], the global index of hippocampal functioning [$t(23) = -5.000$, $p = .000$], and the global index of explicit memory [$t(23) = -5.018$, $p = .000$]. The PD group also scored below the NC group on d' [$t(28) = 3.241$, $p = .002$], the global index of hippocampal functioning [$t(31) = 6.233$, $p = .000$], and the global index of explicit memory [$t(31) = 5.941$, $p = .000$]. The PD group scored higher (poorer performance) on the MCST composite score than the OD group [$t(23) = 2.416$, $p = .012$] and the NC group [$t(31) = -3.373$, $p = .001$].

These analyses were also conducted with age as a covariate because there were group differences in age. There was no longer a significant difference between the PD and OD groups on d'. This was the only change in the pattern of results.

Symptom Scale Ratings The PD group had significantly higher ratings than the OD group on the Positive Symptoms scale [$t(23) = 1.854$, $p = .039$], the Disorganized Symptoms scale [$t(23) = 2.526$, $p = .010$], and the Overall Symptoms scale [$t(23) = 3.160$, $p = .002$]. The diagnostic groups did not differ on negative symptoms.

Cortisol There were no diagnostic group differences on the measures of cortisol. However, it is possible that psychotropic medication was masking group differences, given evidence that antipsychotics reduce cortisol levels (Walker and Diforio 1997). In addition, some studies have evidenced hypercortisolemia in depressed patients (Carpenter and Bunney 1971; Deuschle et al 1998). More specifically, Galard et al (1991) and Gotthardt et al (1995) showed significantly higher basal levels of cortisol in depressed patients relative to NC subjects. The inclusion of a large majority of subjects with a history of depression in the OD group might therefore account for the absence of a significant difference in cortisol secretion between the PD and OD groups.

Some psychiatric populations (viz., depressed patients) have also been shown to exhibit hypersecretion of cortisol during the afternoon (Christie et al 1986; Seckl et al 1991). Given the diagnostic nature of the OD group subjects, restriction of the cortisol samplings to morning hours in this study may account for the lack of significant group differences in cortisol.

Results

The Relation between Cortisol and Cognitive Performance

All correlational analyses were conducted using one-tailed tests because of the directional nature of the hypothesized relations among the examined variables. Pearson correlation analyses conducted across the total sample (PD group, OD group, and NC group) indicated that explicit memory and hippocampal functioning were negatively correlated with time 3 cortisol (Table 3). Hippocampal functioning was also negatively correlated with time 2 cortisol. The pattern of results indicates that higher cortisol was associated with poorer performance. Performance on the MCST, as indexed by the composite score, was not correlated with any of the cortisol measures.

Correlational analyses examining discrete aspects of memory performance—namely, immediate, short-term, and long-term memory—were also conducted (Table 4). Results indicated that time 1 cortisol was not associated with any of the three derived subcomponents of memory in either the total sample or the NC group. Time 2 cortisol

Table 4. Correlation Coefficients Relating Cortisol with Immediate, Short-Term, and Long-Term Memory for Total Sample, Psychotic Disorder Group, Other Disorders Group, and Normal Control Group

	Index				
Memory	Cortisol at time 1	Cortisol at time 2	Cortisol at time 3	Mean cortisol	Cortisol slope
Total sample[a]					
Immediate	.055	−.280[b]	−.347[b]	−.191	−.277[b]
Short term	.028	−.179	−.312[b]	−.152	−.221
Long term	.052	−.254	−.334[b]	−.172	−.255
Normal control[c]					
Immediate	−.206	−.860[d]	−.758[d]	−.670[d]	−.768[d]
Short term	.203	−.504[b]	−.398	−.222	−.346
Long term	.044	−.734[d]	−.581[b]	−.446[b]	−.570[b]
Psychotic disorders[e]					
Immediate	.148	.146	.083	.160	.147
Short term	−.186	−.022	−.222	−.161	−.159
Long term	−.104	.065	.031	−.015	.016
Other disorders[f]					
Immediate	.427	.361	−.343	.367	.155
Short term	.146	.351	−.369	.116	−.022
Long term	.405	.118	−.644	.141	−.200

[a] $n = 40$.
[b] $p < .05$, one-tailed test.
[c] $n = 15$.
[d] $p < .01$, one-tailed test.
[e] $n = 18$.
[f] $n = 7$.

was significantly correlated with all three memory variables in the NC group, but with only immediate recall in the total sample. Time 3 cortisol was significantly correlated with all three memory variables in the total sample, but with only immediate and long-term memory in the NC group. Mean cortisol and cortisol slope were significantly correlated with immediate and long-term memory in the NC group. In the total sample, cortisol slope was significantly correlated with immediate memory; no other correlations were significant within this group. There were no significant findings in the PD and OD groups alone. Overall, these results suggests that cortisol levels were associated with immediate, short-term, and long-term memory performance .

It is possible that attentional problems contribute to the observed memory deficits in schizophrenia. The correlational analyses were therefore repeated controlling for attention, as indexed by sensitivity performance on the CPT-Vigil. All of the significant correlations held after covarying for attention. In addition, there were significant negative correlations for cortisol slope with explicit memory and hippocampal functioning, as well as time 2 cortisol with explicit memory, and significant positive correlations for time 2 cortisol, mean cortisol, and cortisol slope with MCST (Table 3). These findings suggest that cognitive impairment attributable to deficits in attention did not account for the relation between cortisol and memory performance. Instead, individual differences in attention were obscuring the relations of cortisol with memory and executive functioning.

The above analyses were repeated with the PD group alone (Table 5). Results indicated no significant correlations for cortisol with explicit memory, hippocampal functioning, or MCST performance. After covarying for attention, there was a trend toward a negative correlation for time 2 cortisol with hippocampal functioning, as well as a positive correlation for time 2 cortisol and cortisol slope with MCST performance.

The majority of the findings among the PD group were consistent with findings among the total sample in that, although they were of lesser magnitude, they were in a similar direction. Findings in the total sample, and to a lesser degree in the PD group, suggest that increased cortisol secretion, particularly those measures presumed to reflect baseline cortisol, is associated with impaired performance on cognitive measures indexing hippocampal functioning.

The Relation between Cortisol and Symptoms

Age was negatively correlated with time 1 cortisol ($r = -.451$, $p = .030$) and mean cortisol ($r = -.410$, $p = .045$) within the PD group. Therefore, correlational analyses of

Table 5. Correlation Coefficients and Partial Correlation Coefficients Relating Cortisol with Explicit Memory and Hippocampal Functioning for Psychotic Disorder Group

	Index				
	Cortisol at time 1	Cortisol at time 2	Cortisol at time 3	Mean cortisol	Cortisol slope
Explicit memory[a] (no covariate)	.039	.042	−.096	.012	−.012
Explicit memory[b] (with CPT sensitivity as covariate)	.000	−.014	−.100	−.032	−.051
Hippocampal functioning[a] (no covariate)	.025	−.132	−.192	−.100	−.144
Hippocampal functioning[b] (with CPT sensitivity as covariate)	−.134	−.428	−.269	−.323	−.362
MCST[a] (no covariate)	−.032	.238	.210	.149	.202
MCST[b] (with CPT sensitivity as covariate)	.146	.634[c]	.313	.432	.484[d]

CPT, Continuous Performance Test; MCST, Modified Wisconsin Card Sorting Test.
[a] $n = 18$.
[b] $n = 12$.
[c] $p < .01$, one-tailed test.
[d] $p < .05$, one-tailed test.

cortisol with symptom severity in the PD group controlled for age for these two measures of cortisol (Table 6).

The pattern of results indicated that higher cortisol levels were associated with more severe symptoms (Table 6). Time 1 cortisol was positively correlated with disorganized and overall symptoms, and mean cortisol was correlated with positive and overall symptoms. After covarying for age, these findings held and mean cortisol was additionally correlated with disorganized symptoms. In addition, time 2 cortisol was correlated with positive symptoms and time 3 cortisol was correlated with positive, disorganized, and overall symptoms. Higher cortisol slope was linked with higher ratings of positive and overall symptoms.

Table 6. Correlation Coefficients and Partial Correlation Coefficients Relating Cortisol with Symptom Scale Ratings, for Psychotic Disorder Group

	Index			
	Symptom scale			Overall
Cortisol	Positive	Negative	Disorganized	Symptoms
Cortisol at time 1 (no covariate)	.151	.123	.519[a]	.434[a]
Cortisol at time 1 (with age as a covariate)	.285	−.038	.718[b]	.467[a]
Cortisol at time 2 (no covariate)	.419[a]	.118	.041	.335
Cortisol at time 3 (no covariate)	.733[b]	.159	.379[a]	.726[b]
Mean cortisol (no covariate)	.461[a]	.156	.335	.559[b]
Mean cortisol (with age as a covariate)	.617[b]	.018	.534[a]	.599[a]
Cortisol slope (no covariate)	.570[b]	.161	.317	.601[b]

$n = 18$.
[a] $p < .05$, one-tailed test.
[b] $p < .01$, one-tailed test.

The Relation between Cognitive Performance and Symptoms

First-order correlations revealed that none of the symptom dimensions was associated with the three cognitive indices. After covarying for attention, however, positive symptoms were negatively correlated with hippocampal functioning ($r = -.729$, $p = .002$) and positively correlated with MCST performance ($r = .841$, $p = .000$). Thus, higher symptom ratings were associated with poorer performance.

The Relation of Cortisol and Task Performance with Symptoms

Stepwise regression analyses were conducted across all subjects with psychotic disorders. Memory performance, hippocampal functioning, MCST performance, and all measures of cortisol were entered as predictor variables. The only significant predictors of symptom severity were time 1 and time 3 cortisol. Time 1 cortisol accounted for 26.9% of the variance in Disorganized Symptom scale ratings. Time 3 cortisol accounted for 53.7% of the variance in Positive Symptom scale ratings and 52.7% of the variance in Overall Symptom scale ratings.

Discussion

This study was designed to examine the relations among memory, cortisol release, and symptom expression in patients with psychotic disorders. In general, the results provide modest support for the hypothesis that elevations in cortisol secretion are associated with deficits in explicit memory performance. Among patients with psychotic

disorders, cortisol shows a strong positive relation with the severity of symptoms, especially positive symptoms.

The Relation between Cortisol and Cognitive Task Performance

Previous research has demonstrated an inverse association between cortisol secretion and memory (e.g., Lupien et al 1994; Seeman et al 1997). Current findings of an inverse relationship of cortisol levels at times 2 and 3 (presumably reflective of basal levels of cortisol) with task performance in the total sample are consistent with these results. Thus, it appears that cortisol levels measured after acclimation to the research setting are most strongly linked with cognitive function. It is possible that this reflects the relation of persistent elevations in circulating corticosteroids with the integrity of various regions of the brain, particularly the hippocampus, which has been implicated in memory function. Some previous research has shown that cognitive testing successfully induces cortisol release (Lupien et al 1997). Thus, it is important to consider that the current finding of an inverse relationship of cortisol with cognitive performance may have been due to heightened cortisol secretion subsequent to cognitive testing.

Although the direction of the relation between cortisol and task performance was similar for the psychotic patients, only two of the coefficients reached statistical significance. It is likely that this is due to insufficient statistical power in this smaller group ($n = 18$) of patients.

The Relation between Cortisol and Symptom Expression

Correlational analyses revealed that heightened cortisol release is associated with increased symptom expression in psychotic disorders. Most of the subjects in the PD group were medicated with or previously medicated with antipsychotics. Thus, findings of an association of symptoms with cortisol secretion, despite medication effects, are all the more striking.

The findings are not supportive of a stronger association between heightened HPA activity and the deficit symptoms of schizophrenia, as suggested by Tandon et al (1991). Rather, these results suggest that heightened HPA activity is generally associated with overall symptom expression in psychotic disorders. In terms of specific symptom dimensions, cortisol indexing sensitivity to novelty (time 1) and mean cortisol were associated with disorganized symptom severity, whereas "basal" (times 2 and 3) measures of cortisol were associated with positive symptom severity. The association between cortisol and positive symptoms is consistent with several previous findings (Kaneko et al 1992; Keshavan et al 1989; Rybakowski et al 1991). No measures of cortisol were associated with negative symptoms.

This suggests a possible dissociation between positive and disorganized symptoms on the one hand and negative symptoms on the other. More specifically, the pattern of association of positive, negative, and disorganized symptoms with the various measures of cortisol suggests that the symptom dimensions are differentially influenced by 1) basal HPA activity linked with the integrity of the hippocampus versus 2) acute changes in HPA activity in response to novelty or stress, respectively.

The Relation between Cognitive Performance and Symptom Expression

Previous studies of the relation between memory performance and symptom severity have yielded mixed findings. Some showed an inverse relation of memory with negative symptoms (Basso et al 1998; Sullivan et al 1994), disorganized symptoms (Basso et al 1998), or total symptom severity (Sullivan et al 1994). Sullivan et al (1994) found a trend in the relationship between memory and positive symptoms. Other studies found no association between memory and symptom severity (Hoff et al 1992; Schmand et al 1992).

In this study, an index of MCST errors and an index of hippocampal functioning, which incorporates the MCST, were linked with positive symptoms but not with the other three symptom scales. This suggests that positive symptoms are associated with more pronounced impairment on measures of frontal function, rather than measures of memory.

The Relation of Cognitive Performance and Cortisol with Symptoms

Regression analyses indicated that time 1 cortisol predicted disorganized symptoms and time 3 cortisol predicted positive and overall symptom severity. No other measures of cortisol or indices of cognitive functioning (e.g., memory, executive, or hippocampal functioning) predicted symptom severity.

In conclusion, analyses of data from the total sample provided further support for a relationship of cortisol with cognitive functions subserved by the hippocampus. Insufficient statistical power may account for the failure of these relations to reach statistical significance within the group of psychotic patients. However, highly significant relations were found between cortisol levels and the severity of patients' symptoms. It is speculated that this may reflect the ability of cortisol to increase dopaminergic activity. Overall, these findings suggest that abnormalities in the HPA axis and hippocampal system may play a role

in the clinical manifestation of schizophrenia. Additional research on larger samples of patients is warranted.

References

Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney WE (1993): Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. *Arch Gen Psychiatry* 50:178–187.

Al'Absi M, Lovallo WR (1993): Cortisol concentrations in serum of borderline hypertensive men exposed to a novel experimental setting. *Psychoneuroendocrinology* 18:355–363.

Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE (1990): The hippocampus and parahippocampus in schizophrenic, suicide, and control brains. *Arch Gen Psychiatry* 47:1029–1034.

Andreasen NC (1981): *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City: University of Iowa Press.

Andreasen NC (1983): *Scale for the Assessment of Negative Symptoms (SANS).* Iowa City: University of Iowa Press.

Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M (1995): Symptoms of schizophrenia: Methods, meanings, and mechanisms. *Arch Gen Psychiatry* 52:341–351.

Arana GW, Barreira PJ, Cohen BM, Lipinski JF, Fogelson D (1983): The dexamethasone suppression test in psychotic disorders. *Am J Psychiatry* 140:1521–1523.

Bassett JR, Marshall PM, Spillane R (1987): The physiological measurement of acute stress in bank employees. *Int J Psychophysiol* 5:265–273.

Basso MR, Nasrallah HA, Olson SC, Bornstein RA (1998): Neuropsychological correlates of negative, disorganized and psychotic symptoms in schizophrenia. *Schizophr Res* 31:99–111.

Baum A, Grunberg N (1995): Measurement of stress hormones. In: Cohen S, Kessler RC, Gordon LU, editors. *Measuring Stress: A Guide for Health and Social Scientists.* New York: Oxford University Press, 175–192.

Benes FM, Sorensen I, Bird ED (1991): Morphometric analyses of the hippocampal formation in schizophrenic brain. *Schizophr Bull* 17:597–608.

Bilder RM, Bogerts B, Ashtari M, Wu H, Alvir JM, Jody D, et al (1995): Anterior hippocampal volume reductions predict "frontal lobe" dysfunction in first episode schizophrenia. *Schizophr Res* 17:47–58.

Bogerts B, Falkai P, Haupts M, Greve B, Ernst S, Tapernon-Franz U, et al (1990): Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Initial results from a new brain collection. *Schizophr Res* 3:295–301.

Bogerts B, Meertz E, Schonfeldt-Bausch R (1985): Basal ganglia and limbic system pathology in schizophrenia. *Arch Gen Psychiatry* 42:784–791.

Breier A, Buchanan R, Elkashef A, Munson RC, Kirkpatrick B, Gellad F (1992): Brain morphology and schizophrenia: A magnet resonance imaging study of limbic prefrontal cortex and caudate structures. *Arch Gen Psychiatry* 49:921–926.

Buchsbaum MS, Sostek AJ (1980): An adaptive-rate continuous performance test: Vigilance characteristics and reliability for 400 male students. *Percept Mot Skills* 51:707–713.

Carpenter W, Bunney W (1971): Adrenal cortical activity in depressive illness. *Am J Psychiatry* 128:31.

Christie JE, Whalley LJ, Blackwood DHR, Blackburn IM, Fink G (1986): Raised plasma cortisol concentrations are a feature of drug-free psychotics and are not specific for depression. *Br J Psychiatry* 148:58–65.

Colombo C, Abbruzzese M, Livian S, Scotti G, Locatelli M, Bonfanti A, et al (1993): Memory functions and temporal-limbic morphology in schizophrenia. *Psychiatry Res* 50:45–56.

Delis DC, Kramer JH, Kaplan E, Ober BA (1983): *CVLT: California Verbal Learning Test Manual.* San Antonio: Psychological Corp.

Delisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, et al (1991): Brain morphology in first-episode schizophrenic-like psychotic patients: A quantitative magnetic resonance imaging study. *Biol Psychiatry* 29:159–175.

De Quervain DJF, Roozendaal B, Nitsch RM, McGaugh JL, Hock C (2000): Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci* 3:313–314.

Deuschle M, Weber B, Colla M, Depner M, Heuser I (1998): Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: A re-evaluation study. *Stress* 2:281–287.

Eichenbaum H, Schoenbaum G, Young B, Bunsey M (1996): Functional organization of the hippocampal memory system. *Proc Natl Acad Sci U S A* 93:13500–13507.

First MB, Spitzer RL, Gibbon M, Williams JBW (1997): *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P Version 2.0, 4/97 Revision).* Washington, DC: American Psychiatric Press, Biometrics Research Department.

Galard R, Gallart JM, Catalan R, Schwartz S, Arguello JM, Castellanos JM (1991): Salivary cortisol levels and their correlation with plasma ACTH levels in depressed patients before and after the DST. *Am J Psychiatry* 148:505–508.

Gold JM, Randolph C, Carpenter CJ, Goldberg TE, Weinberger DR (1992a): Forms of memory failure in schizophrenia. *J Abnorm Psychol* 101:487–494.

Gold JM, Randolph C, Carpenter CJ, Goldberg TE, Weinberger DR (1992b): The performance of patients with schizophrenia on the Wechsler Memory Scale-Revised. *Clin Neuropsychol* 6:367–373.

Goldberg TE, Ragland JD, Torrey EF, Gold JM, Bigelow LB, Weinberger DR (1990): Neuropsychological assessment of monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry* 47:1066–1072.

Goldberg TE, Torrey EF, Berman KF, Weinberger DR (1994): Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. *Psychiatry Res* 55:51–61.

Goldberg TE, Weinberger DR (1995): A case against subtyping in schizophrenia. *Schizophr Res* 17:147–152.

Gotthardt U, Schweiger U, Fahrenberg J, Lauer CJ, Holsboer F, Heuser I (1995): Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. *Am J Physiol* 268:R865–R873.

Hennessy MB, Mendoza SP, Mason WA, Moberg GP (1995): Endocrine sensitivity to novelty in squirrel monkeys and titi monkeys: Species differences in characteristic modes of responding to the environment. *Physiol Behav* 57:331–338.

Hirayasu Y, Shenton ME, Salisbury DF, Dickey CC, Fischer IA, Mazzoni P, et al (1998): Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. *Am J Psychiatry* 155:1384–1391.

Hoff AL, Riordan H, O'Donnell DW, Morris L, DeLisi LE (1992): Neuropsychological functioning of first-episode schizophreniform patients. *Am J Psychiatry* 149:898–903.

Jeste DV, Lohr JB (1989): Hippocampal pathologic findings in schizophrenia. A morphometric study. *Arch Gen Psychiatry* 46:1019–1024.

Kaneko M, Yokoyama F, Hoshino Y, Takahagu K, Murata S, Watanabe M, et al (1992): Hypothalamic pituitary adrenal axis function in chronic schizophrenia: Association with clinical features. *Neuropsychobiology* 25:1–7.

Keshavan MS, Brar J, Ganguli R, Jarrett D (1989): DST and schizophrenic symptomatology. *Biol Psychiatry* 26:847–858.

Kiess W, Meidert A, Dressendorfer RA, Schriever K, Kessler U, Konig A, et al (1995): Salivary cortisol levels throughout childhood and adolescence: Relation with age, pubertal stage and weight. *Pediatr Res* 37:502–506.

Kirschbaum C, Hellhammer DH (1989): Salivary cortisol in psychobiological research: An overview. *Neuropsychobiology* 22:150–169.

Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH (1996): Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci* 58:1475–1483.

Kovelman JA, Scheibel AB (1984): A neurohistological correlate of schizophrenia. *Biol Psychiatry* 19:1601–1621.

Laudat MH, Cerdas S, Fournier C, Guiban D, Guilhaume B, Luton JP (1988): Salivary cortisol measurement: A practical approach to assess pituitary-adrenal function. *J Clin Endocrinol Metab* 66:343–348.

Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al (1992): Quantitative magnetic resonance imaging in temporal lobe epilepsy: Relationship to neuropathology and neuropsychological function. *Ann Neurol* 31:629–637.

Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NPV, Meaney MJ (1994): Basal cortisol levels and cognitive deficits in human aging. *J Neurosci* 14:2893–2903.

Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, et al (1997): Stress-induced declarative memory impairment in healthy elderly subjects: Relationship to cortisol reactivity. *J Clin Endocrinol Metab* 82:2070–2075.

McNicol D, Willson RJ (1971): The application of signal detection theory to letter recognition. *Aust J Psychol* 23:311–315.

Nelson HE (1976): A modified card sort test sensitive to frontal lobe defects. *Cortex* 12:313–324.

Nestor PG, Shenton ME, McCarley RW, Haimson J, Smith RS, O'Donnell B, et al (1993): Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. *Am J Psychiatry* 150:1849–1855.

Newcomer JW, Craft S, Askins K, Hershey T, Bardgett ME, Csernansky JG, et al (1998): Glucocorticoid interactions with memory function in schizophrenia. *Psychoneuroendocrinology* 23:65–72.

Newcomer JW, Craft S, Hershey T, Askins K, Bardgett J (1994): Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J Neurosci* 14:2047–2053.

Newcomer JW, Faustman WO, Whiteford HA, Moses JA Jr, Csernansky JG (1991): Symptomatology and cognitive impairment associate independently with post-dexamethasone cortisol concentrations in unmedicated schizophrenic patients. *Biol Psychiatry* 29:855–864.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL (1999): Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry* 56:527–533.

Rao VP, Krishnan RR, Goli V, Saunders WB, Ellinwood EH, Blazer DG, et al (1989): Neuroanatomical changes and hypothalamic-pituitary-adrenal axis abnormalities. *Biol Psychiatry* 26:729–732.

Rybakowski J, Linka M, Matkowski K, Kanarkowski R (1991): Dexamethasone suppression test and the positive and negative symptoms of schizophrenia. *Psychiatr Pol* 25:9–15.

Sapolsky RM, McEwen BS (1986): Stress, glucocorticoids, and their role in degenerative changes in the aging hippocampus. In: Crook T, Bartus R, Ferris S, Gershon S, editors. *Treatment Development Strategies for Alzheimer's Disease.* Madison, CT: Mark Powley, 151–171.

Sapolsky RM, Uno H, Rebert CS, Finch CE (1990): Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 10:2897–2902.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, et al (1994): Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. *Arch Gen Psychiatry* 51:124–131.

Schatzberg AF, Rothschild AJ (1988): The roles of glucocorticoid and dopaminergic systems in delusional (psychotic) depression. *Ann N Y Acad Sci* 537:462–471.

Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO (1985): A corticosteroid/dopamine hypothesis for psychotic depression and related states. *J Psychiatry Res* 19:57–64.

Schmand B, Brand N, Kuipers T (1992): Procedural learning of cognitive and motor skills in psychotic patients. *Schizophr Res* 8:157–170.

Seckl JR, Campbell JC, Edwards CRW, Christie JE, Whalley LJ, Goodwin GM, Fink G (1991): Diurnal variation of plasma corticosterone in depression. *Psychoneuroendocrinology* 15: 485–488.

Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW (1997): Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *J Clin Endocrinol Metab* 82:2458–2465.

Sharma RP, Pandey GN, Janicak PG, Peterson J, Comaty JE, Davis JM (1988): The effect of diagnosis and age on the DST: A meta-analytic approach. *Biol Psychiatry* 24:555–568.

Shipley JE, Alessi NE, Wade SE, Haegle AD, Helmbold B

(1992): Utility of an oral diffusion sink (ODS) device for quantification of saliva corticosteroids in human subjects. *J Clin Endocrinol Metab* 74:698–700.

Squire LR (1987): *Memory and Brain.* New York: Oxford University Press.

Squire LR (1992): Memory and the hippocampus. A synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 99:195–231.

Starkman MN, Gebarski SS, Berent S, Schteingart DE (1992): Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiatry* 32:756–765.

Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR (1990): Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med* 322:789–794.

Sullivan EV, Shear PK, Zipursky RB, Sagar HJ, Pfefferbaum A (1994): A deficit profile of executive, memory and motor functions in schizophrenia. *Biol Psychiatry* 36:641–653.

Tandon R, Mazzara C, DeQuardo J, Craig KA, Meador-Woodruff JH, Goldman R (1991): Dexamethasone suppression test in schizophrenia: Relationship to symptomatology, ventricular enlargement, and outcome. *Biol Psychiatry* 29:953–964.

Torres IJ, Flashman LA, O'Leary DS, Swayze V II, Andreasen NC (1997): Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. *Biol Psychiatry* 42:1087–1096.

Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, et al (1999): Hippocampal volume in first-episode psychoses and chronic schizophrenia: A high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry* 56:133–141.

Waldo MC, Cawthra E, Adler LE, Dubester S, Staunton M, Nagamoto H, et al (1994): Auditory sensory gating, hippocampal volume, and catecholamine metaboism in schizophrenics and their siblings. *Schizophr Res* 12:93–106.

Walker EF, Diforio D (1997): Schizophrenia: A neural diathesis-stress model. *Psychol Rev* 104:667–685.

Wechsler D (1987): *Wechsler Memory Scale—Revised.* New York: Psychological Corp.

Weinstein DD, Diforio D, Schiffman J, Walker E, Bonsall R (1999): Minor physical anomalies, dermatoglyphic asymmetries, and cortisol levels in adolescents with schizotypal personality disorder. *Am J Psychiatry* 156:617–623.

Appendix 1. Items in the SANS-SAPS–Derived Symptom Scales

Item no.	Criteria
Positive symptoms	
24	Thoughts of being persecuted by other people
26	Thoughts of sin or guilt
27	Grandiose thoughts
28	Religious thoughts
29	Thoughts concerning the body
30	Ideas and thoughts of self-reference
31	Thoughts of being controlled
32	Thoughts of mind reading
33	Thought broadcasting
34	Thought insertion
48	Hallucinatorylike experiences involving noises or voices
51	Hallucinatorylike experiences concerning the body
52	Hallucinatorylike experiences involving odors/sense of smell
53	Visual hallucinatorylike experiences
Negative symptoms	
1	Facial expressions of emotion
2	Spontaneous movements of arms and legs
3	Expressive gestures
4	Eye contact
5	Emotional responsivity to other people or events
6	Vocal inflections
14	Grooming and hygiene
16	Physical energy
47	Repetitive or stereotyped behavior
Disorganized symptoms	
7	Appropriateness of emotional expressions
36	Loose associations
37	Tangential responses
39	Illogical speech
40	Circumstantial speech
41	Rapid speech
42	Distractible speech
43	Clanging
44	Clothing and appearance

SANS, Schedule for Assessment of Negative Symptoms; SAPS, Schedule for Assessment of Positive Symptoms.