Cortisol Dysregulation and Cognitive Impairment in Abstinent Male Alcoholics

Austin L. Errico, Andrea C. King, William R. Lovallo, and Oscar A. Parsons†

Background: Alcoholics have impaired cortisol response to stress, indicating dysregulation in the extrahypothalamic systems responsible for activating cortisol secretion in response to stressor exposure. There is a growing literature indicating a relationship between hypothalamic-pituitary-adrenocortical axis activity and neurocognitive functioning. This study examined the hypothesis that dysregulation of the hypothalamic-pituitary-adrenocortical axis may be associated with some neuropsychological impairments in alcoholics.

Methods: Serum cortisol was obtained during cognitive testing and after exposure to cold pressor and mental arithmetic stress in 48 male alcoholics abstinent for 32 ± 6.7 days and in 30 controls; cortisol was also obtained from 18 of the alcoholic patients during withdrawal. Neurocognitive tasks included the Wechsler Memory Scale and Wisconsin Card Sorting Test. Relationships among alcoholics’ cognitive test scores, cortisol levels, and drinking practices were examined by correlation and regression analyses.

Results: Verbal memory deficits were more severe in alcoholics who had more withdrawals and ingested a higher typical quantity of alcohol during the prior year (p < 0.05). Higher levels of cortisol during withdrawal, an index of withdrawal severity, were associated with more errors on the Wisconsin Card Sorting Test (p < 0.005). As previously reported, the alcoholics had lower cortisol levels after stress compared with controls. Lower poststress cortisol levels were associated with poorer logical memory on the Wechsler Memory Scale and more errors on the Wisconsin Card Sorting Test (p < 0.05). Among controls, memory deficits occurred only in relation to higher poststress cortisol levels.

Conclusions: Poorer cognitive performance in alcoholics was related to more withdrawals, heavier alcohol consumption, and higher cortisol levels during a recent withdrawal. Alcoholics’ cognitive impairment was also related to attenuated stress cortisol responses. Altered stress regulation of the hypothalamic-pituitary-adrenal axis should be studied further as a potential factor related to impaired cognitive function in recovering alcoholics.

Key Words: Alcoholism, Cortisol, Spatial Memory, Problem Solving, Stress Response.

Alcoholics have functional impairments in learning, memory, abstracting, and problem-solving (Parsons, 1998). These may result from the brain’s exposure to alcohol, or they may be secondary to other effects, such as alcoholic liver dysfunction (Tarter et al., 1986) or altered hypothalamic-pituitary-adrenocortical (HPA) regulation (Adinoff et al., 1998; Costa et al., 1996; Van Thiel and Lester, 1978). This study investigated the hypothesis that there may be associations between indicators of cortisol dysregulation and cognitive impairments in recently detoxified male alcoholics.

Dysregulation of HPA function has been related to cognitive deficits in nonalcoholic populations (Lupien et al., 1998, 1999). Patients with chronically increased cortisol due to Cushing’s disease (Mauri et al., 1993; Starkman et al., 1981) or clinical depression (Rubinow et al., 1984) have cognitive impairments that resolve with successful treatment. Prolonged cortisol increases in the elderly are associated with hippocampal shrinkage and declarative memory impairment (Lupien et al., 1998). In contrast to these chronic studies, acute cortisol increases have been associated with both improved and impaired memory (Buchanan and Lovallo, 2001; de Quervain et al., 2000; Lupien and McEwen, 1997). Therefore, memory and learning may vary both as a function of long-term regulation of cortisol secretion and in relation to acute changes.

This study addressed the question of whether signs of altered cortisol regulation may accompany cognitive im-
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PAIRMENTS in alcoholics. Cortisol is increased during times of heavy alcohol intake and withdrawal (Iranmanesh et al., 1989). These cortisol increases could have negative effects on the hippocampus and higher cortical systems (Adinoff et al., 1998), particularly if they are severe or protracted. In a prior study by our group, the number of reported withdrawals from alcohol (abstinence ≥24 hr) during the prior year was a significant predictor of poorer cognitive performance after detoxification, particularly on tests of visual-spatial memory (Glenn et al., 1988). The first aim of this study was to replicate these findings in an independent sample of postwithdrawal alcoholics. Our second aim was to test cognitive performance in relation to cortisol levels during the patient’s most recent withdrawal at detoxification.

Although a normal diurnal pattern of cortisol secretion is re-established after approximately 8 days of abstinence from alcohol (Adinoff et al., 1991), remitted alcoholics show attenuated cortisol responses to exogenous corticotropin-releasing factor (Adinoff et al., 1990) and laboratory stressors (Bernardy et al., 1996; Errico et al., 1993; Lovallo et al., 2000) at 21 to 28 days of abstinence. This hypersensitivity indicates altered HPA regulation, which may in turn signal cognitive alterations. Our third aim was therefore to measure cortisol responses to laboratory stressors in relation to performance on tests of memory and problem-solving. In accord with these aims, we measured drinking behaviors in the past year and cortisol levels during a recent withdrawal and in response to laboratory stressors in recently detoxified alcoholics undergoing neuropsychological testing (Errico et al., 1992).

METHOD

Subjects

The study originally enrolled 52 male alcoholic inpatients recruited from treatment programs in the Oklahoma City area and 32 male nonalcoholic community controls. Due to difficulties with blood sampling and incomplete neuropsychological data for four alcoholics and two control subjects, the final sample size for the study consisted of 48 alcoholics and 30 nonalcoholic controls.

Participants were free of neurological disease, major psychiatric disorders, endocrine dysfunction, liver disease, and other medical conditions or medications that could affect steroid metabolism or cognitive functioning. Persons were excluded if they scored in the clinical ranges of the Beck Depression Inventory (Beck et al., 1988) or Spielberger State Anxiety Inventory (Spielberger et al., 1970). Patients all met DSM-III-R criteria for alcohol dependence (American Psychiatric Association, 1987). All subjects signed an informed consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and Veterans Affairs Medical Center and were paid for participation.

Procedure

Withdrawal Cortisol. On the morning after admission for detoxification, a single blood sample was taken by the unit nurse on a subgroup of 18 alcoholics in the study who had their last occurrence of alcohol intake within 5 days of admission. Written informed consent was obtained from each patient on the evening of admission. The blood sample was drawn at approximately 8:00 AM on the first morning after admission to the Veterans Affairs alcoholic treatment unit. This sample was used to assess serum cortisol levels during this approximate early withdrawal phase.

Table 1. Means (SDs) for Cortisol Levels in Alcoholics and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alcoholics</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal cortisol*</td>
<td>17.54 (5.2)</td>
<td>—</td>
</tr>
<tr>
<td>Cortisol 1</td>
<td>14.99 (4.7)</td>
<td>14.99 (4.3)</td>
</tr>
<tr>
<td>Cortisol 2</td>
<td>11.77 (4.4)</td>
<td>11.50 (4.0)</td>
</tr>
<tr>
<td>Cortisol 3</td>
<td>9.45 (4.5)</td>
<td>9.51 (3.0)</td>
</tr>
<tr>
<td>Cortisol 4</td>
<td>10.40 (3.7)</td>
<td>11.25 (4.0)</td>
</tr>
<tr>
<td>Cortisol 5</td>
<td>10.50 (3.85)</td>
<td>14.35 (5.5)*</td>
</tr>
</tbody>
</table>

*p < 0.001.

Test Protocol. Patients were tested for stress reactivity and neurocognitive performance during days 21 to 28 of treatment, an average of 32 ± 6.7 days after withdrawal. Subjects entered the laboratory individually at 8:00 AM and gave informed consent. At 8:15 AM, a Teflon® (Teflon, Dupont, Wilmington, DE) catheter with a heparin lock was placed into a forearm vein by a trained technician. Blood was drawn into serum-separator Vacutainer® tubes (Becton Dickinson, East Rutherford, NJ) at 8:15 AM, 9:30 AM (during cognitive testing), 10:00 AM (after testing), 10:30 AM (at the end of the stressors), and 11:00 AM (30 min after the stressors). At each blood draw, subjects reported their mood states by using a modified Subjective States Questionnaire (Lundberg and Frankenhaeuser, 1978). After the protocol, subjects were administered a quantity/quality interview (Cahalan et al., 1969) and a timeline follow-back calendar (Sobell et al., 1979) to assess drinking behavior over the past year. As in our past studies, for alcoholics, a withdrawal from alcohol was defined as a 24-hr period of abstinence after a drinking day, as assessed by the timeline follow-back method. This period of time (first 24 hr after alcohol consumption) was chosen for ease of recall as well as representing the most significant interval for physiologic changes corresponding to early alcohol deprivation and withdrawal symptoms.

Neuropsychological Testing. The participants completed the (1) Wechsler Memory Scale, immediate and delayed logical memory for paragraphs (Wechsler, 1945); (2) Wechsler immediate and delayed visual reproduction subtests (versions I and II; Wechsler, 1945); (3) Rey’s Complex Figure, copying and recall (Rey, 1941); (4) Hebb’s Recurring Digits Test (Milner, 1970); (5) Corsi’s Block Tapping Test (Milner, 1971); and (6) the Wisconsin Card Sorting Test (Heaton, 1981). All tests were scored according to published procedures.

Stressors. The mental arithmetic and cold pressor tasks are aversive tasks, and they induce cortisol responses and sympathetic nervous system outflow—both indicators of stress (Lovelock, 1975; Lundberg and Frankenhaeuser, 1980; Seals, 1990). During mental arithmetic, the subject performed 20 min of serial additions while listening to distracting white noise (85 dBa) through earphones. The subject was given a two-digit number and was asked to add the digits and to add this sum to the original number, in repeated fashion. Performance was monitored by the experimenter, and after each error the subject was told to return to the previous correct answer and to continue. The cold presser test followed immediately and required the subject to immerse his hand in a container of ice water for 90 sec. As reported previously, the groups had nearly identical morning cortisol values before the start of the test procedures; however, the 22 min of combined stressors produced a significant increase in stress cortisol response in the controls, but not in the alcoholics, who showed a blunted stress response (see Table 1). The dependent variable thus chosen was this poststress measure (measured 40 min after the onset of the stressors), which may be the most sensitive indicator of alcoholics’ hyporeactive HPA stress response.

Cortisol Assays. Blood samples were centrifuged for 10 min within 5 hr of collection, serum was drawn off, and specimens were stored at −20°C until assayed. Total cortisol concentration was quantified by using the Coat-A-Count Kit® (Diagnostic Products Corp., Los Angeles, CA), a solid-phase radioimmunoassay, in which 125I-labeled cortisol competes for a fixed time with specimen cortisol for antibody sites. The antibody is immobilized to the wall of a polypropylene tube, and decanting the supernatant terminates the competition and isolates the antibody-bound
Table 2. Demographics, Drinking Behaviors, and Psychological Test Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alcoholics (n = 48)</th>
<th>Controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.2 (7.3)</td>
<td>37.0 (9.6)</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.9 (1.9)</td>
<td>13.0 (1.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.0 (11.2)</td>
<td>84.8 (11.3)</td>
</tr>
<tr>
<td>Beck Depression Index</td>
<td>5.2 (5.8)*</td>
<td>2.4 (3.4)</td>
</tr>
<tr>
<td>Anxiety inventory</td>
<td>49 (7.7)**</td>
<td>44 (6.2)</td>
</tr>
<tr>
<td>Shipley Verbal Age (years)</td>
<td>17 (1.9)**</td>
<td>18 (1.4)</td>
</tr>
<tr>
<td>Typical quantity (oz)</td>
<td>14.5 (8.2)**</td>
<td>13 (1.2)</td>
</tr>
<tr>
<td>Chronicity (years)</td>
<td>15.1 (7.5)</td>
<td>—</td>
</tr>
</tbody>
</table>

Values shown are mean (SD).
Anxiety inventory, Spielberger State Anxiety Inventory.
Significance levels were based on group comparisons using Student’s t test or \( \chi^2 \) where appropriate.

- \( p < 0.05 \)
- \( **p < 0.01 \)
- \( ***p < 0.001 \)

fraction of radiolabeled cortisol. A gamma counter then yields a number of gamma counts that converts by way of a calibration curve to a measure of the cortisol present in the subject’s specimen. The assay has a minimum detection limit of 0.2 \( \mu \)g/dl.

Statistical Analyses

Groups were first compared on demographics and neuropsychological performance measures by using Student’s t test. Tests showing alcoholics to be impaired relative to controls were retained for analyses of associations between cortisol and cognitive deficits. As stated previously, only 18 of the patients were admitted during the approximate period reflective of alcohol withdrawal (all of these had had their last drink \( \leq 5.5 \) days before their admission). Because of this small number of patients, relationships between cortisol and cognitive deficits. Scores on the five tests that alcohol showed impaired performance were used the dependent variables and number of withdrawal days, typical quantity, and poststress cortisol levels were used as the independent variables. Among the controls, relationships between poststress cortisol and cognitive performance were also explored by using Pearson’s \( r \) because the variables used in the alcoholics’ model either had too little variance (typical alcohol quantity) or were not appropriate factors (withdrawals) in the nonalcoholic control group.

RESULTS

The groups did not differ in most of the major demographic and socioeconomic indicators, such as age, education levels, racial composition, height, and weight, although the patients had a lower Shipley Verbal Age than did the controls (see Table 2). As expected, the alcoholics were higher in typical quantity of ethanol consumed (\( t = 7.19; \ p < 0.0001 \)) and in self-reported symptoms of depression and anxiety (\( r > 2.40; \ p < 0.02 \)). None of the patients scored in the clinical range on either measure of affect. Alcoholic patients with and without withdrawal cortisol specimens did not differ in age, education, adiposity index, years of alcoholism, typical quantity of ethanol consumed, withdrawals in the past year, or reported depression or anxiety. These subsamples were therefore considered comparable.

In terms of neuropsychological performance (Table 3), alcoholics performed more poorly than controls on the Wechsler immediate and delayed logical memory and the Wechsler delayed visual reproduction subtest, but not the immediate visual reproduction test. Alcoholics also made more errors on the Wisconsin Card Sorting Test than controls. Alcoholics had poorer performance than controls on the memory portion of the Rey Complex Figure Test \( [t(77) = 2.03; \ p = 0.047] \). The groups did not differ on the Corsi Block Tapping Test or the Hebb Recurring Digits Test (see Table 3). Because our objective was to investigate the relationship of cortisol dysregulation to cognitive impairments, test measures on which the alcoholics and controls did not significantly differ were omitted from further analyses.

Aim 1 was to replicate our earlier report of a significant relationship between numbers of withdrawals and cognitive deficits in alcoholics. The alcoholics reported \( 21 \pm 22.9 \) (mean \pm range) withdrawals in the 12 months before admission, and this figure is similar to that of the male alcoholics in our previous study (\( 21 \pm 22.0; \) Glenn et al., 1988). In this study, the number of withdrawals was the strongest predictor of impairments in immediate (\( p < 0.04 \)) and delayed verbal memory (\( p < 0.01; \) Table 3), but not problem-solving. Typical quantity consumed also predicted poorer immediate (\( p < 0.03 \)), but not delayed (\( p = 0.10 \)), verbal memory.

Our second aim was to examine associations between cortisol increases during the most recent withdrawal and cognitive function. First, there was a significant increase in cortisol during withdrawal (i.e., the approximate indicator of alcohol withdrawal on the morning after admission) compared with the baseline morning cortisol sample on the subsequent laboratory testing session [\( 17.54 \pm 13.95 \mu \text{g/dl}; \ t(17) = 3.07; \ p < 0.01; \) derived from \( n = 18 \) alcoholics with both samples]. Second, the withdrawal difference score was significantly correlated with errors on the Wisconsin Card Sorting Test (\( r = 0.63; \ p = 0.005 \)). No other significant correlations were found between this cortisol difference score and neuropsychological test scores.

Our third aim was to explore the associations between poststress cortisol and cognitive function in alcoholics. Multiple regression analyses revealed that attenuated poststress cortisol was significantly associated with greater problem-solving errors on the Wisconsin Card Sorting Test (\( p = 0.02; \) Table 4), even after the effects of typical alcohol quantity were taken into account. Attenuated poststress cortisol response was also a marginally significant factor associated with worse delayed memory for paragraphs on the Wechsler Memory Scale (\( p = 0.06; \) Table 4), even after the effects of the number of withdrawals and alcohol quantity were taken into account. Although reduced cortisol stress responsivity in recovering alcoholics was associated with difficulties in these specific tests of memory and
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Regression models to predict figural memory (Wechsler Memory Scale, delayed figural memory; Rey Complex Figure, delayed recall) were nonsignificant and excluded for brevity.

NS, not significant.

DISCUSSION

Consistent with previous studies, the alcoholics performed more poorly than controls on select tests of memory and problem solving. On some of these tests where alcoholics demonstrated impairment, the deficits were associated with the number of withdrawal days, alcohol intake during the past year, and indicators of cortisol dysregulation at withdrawal or during laboratory stress after several weeks of abstinence. However, this finding was not ubiquitous, and the potential relationships between cognitive deficits and indicators of abnormal cortisol secretion in the alcoholics must be viewed as preliminary and our interpretation as speculative. Additionally, these results do not allow conclusions as to the directions of the associations between drinking, cortisol regulation, and cognitive function. It is possible that heavy drinking impairs cognitive function and alters cortisol regulation in parallel. However, the results may provide leads for future studies of the role of endocrine dysregulation and cognitive impairment in alcoholism.

In relation to aim 1, the number of withdrawals a patient experienced over the prior year predicted verbal memory impairment after detoxification, confirming a previous finding (Glenn et al., 1988). Although several deleterious processes may occur during withdrawal from heavy drinking, we may speculate that patients with more frequent withdrawals might have been exposed to higher cumulative levels of cortisol from periodic hypersecretion and loss of diurnal rhythm at those times (Iranmanesh et al., 1989). The potential effects of increased cortisol exposure are consistent with evidence of declarative memory loss in problem-solving, it was not significantly related to the remaining three tests examined (immediate verbal memory, delayed figural recall, and memory for the Rey figure). For the visuospatial tests, there was no significant association with impaired performance.

Finally, in agreement with other studies but in contrast to the findings in alcoholics, among the controls, higher poststress cortisol levels were related to worse memory performance, as indexed by the immediate \( r = -0.47; p = 0.008 \) and delayed \( r = -0.33; p = 0.06 \) visual reproduction tests of the Wechsler Memory Scale. No other significant associations were found in the nonalcoholic controls with respect to cortisol and performance.

Table 3. Memory and Problem-Solving Scores in Alcoholics and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alcoholics ( n = 48 )</th>
<th>Controls ( n = 30 )</th>
<th>( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. errors</td>
<td>29.0 (23.8)</td>
<td>18.1 (21.3)</td>
<td>2.10</td>
<td>0.04*</td>
</tr>
<tr>
<td>Rey Complex Figure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copying</td>
<td>33.2 (2.2)</td>
<td>32.0 (3.6)</td>
<td>1.74</td>
<td>0.09</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>20.3 (5.4)</td>
<td>22.3 (5.3)</td>
<td>2.03</td>
<td>0.05*</td>
</tr>
<tr>
<td>Corsi Repeated Block Design</td>
<td>3.8 (2.8)</td>
<td>4.8 (2.4)</td>
<td>1.58</td>
<td>0.12</td>
</tr>
<tr>
<td>Hebb Repeated Recurring Digits</td>
<td>3.6 (2.7)</td>
<td>3.7 (2.9)</td>
<td>0.14</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Entries show mean (SD).  
* \( p < 0.05 \).  
** \( p < 0.01 \).

Table 4. Multiple Regression Analyses Predicting Alcoholics’ Neuropsychological Deficits

<table>
<thead>
<tr>
<th>Variable</th>
<th>( B )</th>
<th>SEB</th>
<th>( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal days</td>
<td>-0.05</td>
<td>0.14</td>
<td>-0.40</td>
<td>NS</td>
</tr>
<tr>
<td>Typical quantity</td>
<td>+0.58</td>
<td>0.34</td>
<td>1.70</td>
<td>0.10</td>
</tr>
<tr>
<td>Poststress cortisol</td>
<td>-2.00</td>
<td>0.83</td>
<td>-2.41</td>
<td>0.02</td>
</tr>
<tr>
<td>Model: ( F(3,43) = 3.29; p &lt; 0.05; R^2 = 0.19; ) adjusted ( R^2 = 0.13 ).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed memory for paragraphs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal days</td>
<td>-0.04</td>
<td>0.02</td>
<td>-2.70</td>
<td>0.01</td>
</tr>
<tr>
<td>Typical quantity</td>
<td>-0.07</td>
<td>0.04</td>
<td>-1.66</td>
<td>0.10</td>
</tr>
<tr>
<td>Poststress cortisol</td>
<td>+0.19</td>
<td>0.10</td>
<td>1.90</td>
<td>0.06</td>
</tr>
<tr>
<td>Model: ( F(3,43) = 4.46; p &lt; 0.01; R^2 = 0.24; ) adjusted ( R^2 = 0.18 ).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate memory for paragraphs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal Days</td>
<td>-0.03</td>
<td>0.01</td>
<td>-2.23</td>
<td>0.03</td>
</tr>
<tr>
<td>Typical Quantity</td>
<td>-0.09</td>
<td>0.04</td>
<td>-2.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Poststress Cortisol</td>
<td>+0.08</td>
<td>0.09</td>
<td>0.92</td>
<td>NS</td>
</tr>
<tr>
<td>Model: ( F(3,43) = 3.57; p = 0.02; R^2 = 0.20; ) adjusted ( R^2 = 0.14 ).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
other hypercortisolemic conditions (Lupien and McEwen, 1997). This result was confined to verbal memory; therefore, we did not support the association of withdrawals with visuospatial memory, although further research is suggested, in larger samples and women alcoholics, to more fully examine the role of withdrawal in various aspects of memory performance.

Our second aim was to investigate withdrawal cortisol levels in relation to cognitive performance. Although the number of withdrawals did not relate to problem-solving errors, increased cortisol during withdrawal did relate significantly to a greater number of problem-solving errors on the Wisconsin Card Sort. In contrast to our expectations, withdrawal cortisol was not associated with memory deficits. These findings nonetheless suggest that repeated withdrawals may contribute to cognitive deficits, potentially through the actions of cortisol. Plausible loci for cortisol’s actions include the hippocampus, prefrontal cortex, and cingulate gyrus (Lupien and McEwen, 1997). Future studies are needed with larger sample sizes, the inclusion of women, and more frequent sampling during withdrawal to examine the temporal dynamics of cortisol hypersecretion.

Finally, our third aim was to examine poststress cortisol levels in relation to memory and problem-solving impairment, measured on the same morning, in alcoholics. Lower poststress cortisol levels in the alcoholics were associated with worse delayed verbal memory and more problem-solving errors. In contrast, our nonalcoholic controls with larger cortisol responses were likely to show worse immediate and delayed figural memory.

It is noteworthy that areas of the brain that are essential to memory and problem-solving are also responsive to cortisol. Declarative memory tasks require encoding and retrieval of new material, processes dependent on hippocampal processes (Squire and Zola-Morgan, 1991). The Wisconsin Card Sorting Test calls for periodic response inhibition and adoption of new strategies, which depend on executive processing, an element of working memory associated with the frontal lobes (Goldman-Rakic, 1990; Smith and Jonides, 1999). The hippocampus, prefrontal cortex, and anterior cingulate gyrus are all richly supplied with type 1 and 2 receptors for cortisol (Feldman and Conforti, 1985). It is possible that frequent exposure to high levels of cortisol during bouts of heavy drinking and subsequent withdrawals may have affected these areas in alcoholics and contributed to their deficits. Our results demonstrate partial support for these hypotheses. Variability might have been present in our findings given that our indicators of cortisol dysregulation were approximations of both withdrawal and stress-responsive HPA function, i.e., examining cortisol levels during the most recent withdrawal episode or response to acute laboratory stressors after 1 month of abstinence. More consolidated measurements over a longer time course in abstinent alcoholics or during multiple withdrawal episodes may help to discern these relationships in future investigations.

The results in the nonalcoholic control group are worth some discussion. The contributory role of cortisol in memory is suggested by reports that acute exogenous cortisol administration in stress-related concentrations results in transient working memory decrements in healthy individuals (Kirschbaum et al., 1996; Lupien et al., 1999). Others have reported working memory and declarative memory deficits in persons with large endogenous stress cortisol responses seen in the same test session (al’Absi et al., 1994, 2002; Kirschbaum et al., 1996); these reports parallel the results seen in our study’s nonalcoholic control group. The ability of cortisol to cause memory decrements or improvements (Buchanan and Løvallø, 2001) may depend on specific concentrations, conditions of testing, and other factors (Lupien and McEwen, 1997). Multiple brain areas, including the prefrontal cortex, anterior cingulate gyrus, amygdala, hippocampus, and hypothalamus, are the primary targets of cortisol feedback during the diurnal cycle (primarily via type 1 or mineralocorticoid receptors) and in times of stress (type 2 or glucocorticoid receptors; Helffinger and Newcomer, 2001; Newcomer et al., 1999; Pavlides et al., 1995). In relation to the alcoholics, the possibility that these areas are dysregulated by high cumulative levels of cortisol associated with heavy drinking and frequent withdrawals provides a useful hypothesis for exploring this potential source of alcoholic cognitive deficits (Adinoff et al., 1998). More needs to be determined about the effect of potentially high stress levels of cortisol occurring during withdrawals and the chronic loss of diurnal rhythm and more modest increases accompanying heavy drinking.

Although these results may reflect some consequences of drinking, alternatively, it is also possible that the results could reflect premorbid alterations in HPA, limbic, or central nervous system functions. Kreek (1996) has long held that addiction-prone persons have dysregulations of HPA regulation. Persons at risk for alcohol dependence, by virtue of family history of alcoholism, have shown differential HPA axis reactivity to ethanol (Schuckit and Gold, 1988) and other pharmacological manipulations (King et al., 2002b; Wand et al., 1999) compared with their family history–negative counterparts. Furthermore, HPA hyporesponsiveness to stress in preadolescent boys has been shown to be prognostic of early initiation of drinking (Moss et al., 1995, 1999). This sample of alcoholics included a preponderance of high-risk persons (>80% with a family history of alcoholism); therefore, examination of premorbid risk factors for HPA alterations was not feasible. However, future studies should examine such factors, in addition to heavy drinking history, in studies of HPA dysregulation and memory deficits.

Finally, several limitations to this study are worth mentioning. First, the number of patients providing withdrawal cortisol samples was relatively small ($n = 18$), and the generality of the findings would be increased by additional observations with ongoing withdrawal severity ratings. Sec-
ond, due to constraints while patients were in inpatient detoxification and treatment, only a single cortisol sample during withdrawal was taken. A series of samples taken over 24 hr might be a more sensitive measure for examining later cognitive impairment. Third, cognitive testing was conducted at 4 to 5 weeks after withdrawal. We therefore have no information about the possible recovery of cognitive function with longer periods of abstinence. Fourth, the sample was composed of only men, and the potential for greater alcohol toxicity and consequences of drinking in women (Ashley et al., 1977; Blume, 1986; Hill, 1984; King et al., 2002a; Morgan and Sherlock, 1977) suggests that related observations should be undertaken in this group.

In summary, the results of this study are consistent with the theory that stress hyposecretion of cortisol relates to poorer memory and problem-solving performance in recovering alcoholics. Drinking and withdrawal patterns were also related to cognitive impairments. In contrast, among nonalcoholic controls, hypersecretion of cortisol during stress was related to worse memory performance, in agreement with other reports. Altered regulation of the HPA in alcoholics may result from heavy drinking or may precede it, and these alterations may affect cognitive functioning. Further work will be needed to replicate and extend these findings to women and to longer periods of abstinence, and different methods will be needed to examine potential brain mechanisms. Altered HPA function may provide insights into alcohol-associated deficits in memory and problem solving.

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