Salivary cortisol patterns and cognitive speed in major depression: a comparison with allergic rhinitis and healthy control subjects

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Abstract

Few studies have investigated the relationship between cortisol and cognitive functions other than memory in depression. This study investigated daily salivary cortisol patterns (basal cortisol levels at 08:00, 16:00, and 21:00 h and flatness of the diurnal curve) in relation to cognitive speed and memory. Twenty-seven unmedicated outpatients with major depressive disorder (MDD) were compared with 36 healthy controls and with 20 allergic rhinitis patients, to determine whether effects should be ascribed to MDD or to more general disease-related processes. MDD patients were characterised by a flatter diurnal cortisol curve and by reduced cognitive speed. Flatter cortisol curves were associated with cognitive slowness. However, this relationship is unlikely to be causal; after control for depressive symptoms and group membership, flatness of the diurnal cortisol curve was no longer a significant predictor of cognitive slowness. Thus, MDD and related depressive symptoms appeared to be independently associated with altered cortisol secretory patterns and with decrements in cognitive speed.

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Keywords: Major depression; Allergic rhinitis; Cognitive speed; Memory; Salivary cortisol

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1. Introduction

Major depressive disorder (MDD) is characterised by dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Holsboer, 1995), with approximately 50% of MDD inpatients showing hypercortisolemia. Abnormally low cortisol levels have also been reported, for example in atypical depression (Gold and Chrousos, 1999), as well as flattening of the diurnal secretory curve (Deuschle et al., 1997). In MDD, elevated cortisol levels are associated with memory dysfunction, at least in older people (Lupien et al., 1999; Mitchell, 1995). Chronically elevated levels of cortisol are thought to have a negative effect on the hippocampus, which is crucially implicated in memory functioning (Jameison and Dinan, 2001; Sapolsky, 1993). The vast majority of studies on the influence of glucocorticoids on cognition have focused on geriatric depression. Furthermore, few studies have related cortisol to cognitive functions other than memory; a negative association between global intellectual functioning and daily cortisol levels was found in patients with MDD (Van London et al., 1998), and an association between higher evening cortisol and faster choice reaction time in healthy older men has been reported (Van Niekerk et al., 2001). In MDD, cognitive speed of information processing might be especially relevant, as slowing of the speed of information processing has been reported in both geriatric and younger patients with major depression (Goodwin, 1997; Nebes et al., 2000; Tsourtos et al., 2002). To our knowledge, no studies have been undertaken to specifically address the relationship between cortisol and cognitive speed in MDD.

Since the HPA axis is activated by stress, it is conceivable that the stress that accompanies disease could lead to both altered cortisol levels and cognitive impairment. Altered HPA activity in depression might thus reflect an aspecific effect of disease. Many studies have compared depressive patients with healthy controls. However, healthy controls not only lack psychiatric illness, but they also lack secondary disease-related stress and malaise. It is, therefore, not yet clear whether alterations in cortisol level and in cognitive function are specific features of MDD or reflect non-specific effects of disease. For this reason, the present study compares a group of MDD outpatients to both a healthy control group and to a group of patients with severe symptomatic allergic rhinitis (AR). Like MDD, AR has considerable negative impact on quality of life (Juniper and Guyatt, 1991; Bousquet et al., 1994; Kremer et al., 2001), and individuals with severe complaints are likely to consult regularly with medical specialists. AR is a chronic disease of non-neurological origin, and any abnormalities in cognition or cortisol are not expected to be caused by symptomatic AR itself, but rather by the secondary aspects of not feeling well.

The current study investigates basal salivary cortisol levels over the day in relation to cognitive speed and memory in non-psychotic, young to middle-aged unmedicated MDD outpatients. Since chronic sleep loss can result in higher evening cortisol levels (Leproult et al., 1997; Spiegel et al., 1999), possible effects of subjective early waking...
problems on cortisol were investigated, as well as possible effects of depressive symptoms. We address three questions: (1) Do MDD outpatients show elevated cortisol levels over the day? (2) Are diurnal cortisol levels related to deficits in cognitive speed and memory? (3) Are cortisol patterns and cognitive impairment specific to MDD, or do they reflect more general, disease-related processes?

2. Methods

2.1. Study design

An outpatient group with MDD was compared with two control groups: an outpatient group with severe symptomatic AR and a healthy group. The examination included neuropsychological measures of intelligence, cognitive speed, memory, and self-report measures of mood and other psychological changes, administered in a single session of approximately 1.5–2 h, including a short break. At the end, subjects were instructed how to take samples of saliva at home or at work and were given written instructions concerning the timing and procedures for saliva sampling. Saliva samples were taken on 2 consecutive days directly following the examination. The protocol was reviewed and approved by the Medical Ethical Committee, and subjects gave informed consent. All subjects were paid $10 for participation and received a written report of their neuropsychological results.

2.2. Subjects

The MDD group included 27 outpatients diagnosed by a psychiatrist, following DSM-IV criteria, as having a current episode of major depression. No patient had attempted suicide. This was the first episode for 22 patients; two patients had experienced one earlier depressive episode, and three patients had experienced two earlier episodes. MDD patients who were medication-free when they first visited the clinic were assessed before any pharmacological treatment. Patients in whom medication was to be changed because of inadequate clinical response entered the study after a wash-out period of 2 weeks, or 3 weeks in case of ending fluoxetine-treatment. For inclusion, subjects had to be 18–65 years. Exclusion criteria were current use of any psychotropic medication, other current Axis I psychiatric disorders, neurological disorders, somatic disorders that can affect cognitive function (e.g. diabetes, thyroid dysfunction), and drug or alcohol abuse. No subject had ever received ECT treatment.

The group with symptomatic AR included 20 consecutively assessed outpatients from the University Department of Otorhinolaryngology, Head, and Neck Surgery. Patients with seasonal AR, allergic to grass- and/or tree-pollen, and patients with perennial AR, allergic to house dust mite, were included. Subjects were examined during a symptomatic period. Possible symptoms were nasal secretion, nasal blockage, itching, and sneezing, all self-rated on 4-point severity scales (absent, mild, moderate, or severe). For inclusion, ratings of at least two symptoms as
moderate or severe (an indication of severe AR) and/or a mean score \( \geq 1 \) on the Rhinitis Quality of Life Questionnaire (RQLQ; Juniper and Guyatt, 1991) were required. The RQLQ is a disease-specific questionnaire, which assesses the extent of subjective disturbances by scoring the presence of various rhinitis symptoms and their practical effects. Twenty-eight symptoms, divided into seven subgroups (nasal symptoms, ocular symptoms, general symptoms, sleeping disorders, practical problems, limitations of activity, and emotionality) were evaluated. Scores ranged from 0 (non-existent) to 6 (maximum). The overall score was calculated from the mean values of the 28 symptoms. Other inclusion criteria were age 18–65 years, a positive Radio-Allergo-Sorbent-Test (RAST) for serum-specific immunoglobulin E, and a positive skin prick test for tree and/or grass pollen or for house dust mite allergens. Exclusion criteria were use of psychotropic medication, self-reported history of treatment for neurological or psychiatric disorder, depressive symptoms (a score \( \geq 10 \) on the Beck Depression Inventory (BDI; Beck and Steer, 1993), and drug or alcohol abuse. Any allergy medications (e.g. nasal decongestants, antihistaminics, anticholinergics, sympathomimetics, theophylline preparations) were ended before the assessment took place, with the wash-out period depending on the respective pharmacokinetics.

Thirty-six healthy control subjects were selected from a large pool of healthy control participants in the Maastricht Ageing Study (Jolles et al., 1995). Inclusion and exclusion criteria were the same as for the AR patients, except that the presence of any kind of current allergies or allergies in the past was an additional exclusion criterion for this group.

2.3. Measurements

2.3.1. Basal cortisol levels

On 2 consecutive days at prearranged times in the morning (08:00 h), late afternoon (16:00 h) and evening (21:00 h), subjects collected saliva samples with a cotton dental roll, which was stored in a capped plastic vial (“Salivette”, Sarstedt, Etten-Leur, The Netherlands). Subjects were verbally instructed not to eat, drink, smoke or practice tooth care for 1 h prior to saliva sampling. Subjects were instructed to write down the exact time of cortisol sampling on a paper on which the above mentioned restrictions were also printed. Uncentrifuged samples were frozen at \(-20\, ^\circ C\) until analysis. Salivary cortisol has been shown to be highly correlated with plasma or serum levels; it is largely unbound and represents the free, biologically active fraction of the hormone (Vining and McGinley, 1986). Salivary cortisol levels were determined in duplicate by direct radioimmunoassay, using \(^{125}\)I-cortisol and antiserum made against the 3-CMO–BSA conjugate. The lower detection limit of the assay was 12 ng/dl, with a mean intra-assay coefficient of variation of 4.8%. Dividing by 36.2 converts cortisol values from ng/dl to nmol/l.

2.3.2. Cognitive functioning

As a measure of cognitive speed, parts A, B, and 0 of the Concept Shifting Task (Vink and Jolles, 1985), and parts 1 and 2 of the Stroop-Colour-Word Test (SCWT;
Stroop, 1935) were used. In part A of the Concept Shifting Task, subjects are instructed to cross out as quickly as possible 25 consecutively numbered small circles arranged in a larger circle. Part B is the same for letters. Part 0, in which the subject has to cross out empty circles, assesses the motor speed component. By subtracting scores on part 0 from the other scores, a reliable estimate of the cognitive speed component can be made. Performances on parts A and B (minus part 0) both reflect speed of automatic information processing; scores on those parts were averaged as a measure of cognitive speed (‘CST-speed’). Part 1 of the SCWT involves a card displaying colour names (SCWT-1), and part 2 involves a card displaying coloured patches (SCWT-2), which both have to be read aloud as quickly as possible. SCWT-1 and SCWT-2 both reflect the speed of automatic information processing; scores were averaged as a second measure of cognitive speed (‘SCWT-speed’).

To assess memory storage and memory retrieval, the Visual Verbal Learning Test (VVLT) was used (Brand and Jolles, 1985). In this test, 15 words were sequentially shown on a computer screen, and the subject was asked to recall as many words as possible. This procedure was repeated five times. Scores on the first trial (assessing working memory), the total number of recalled words after five trials, and delayed recall after 20 min (retrieval) were used in the analysis.

2.3.3. Possible confounding variables

We investigated whether an association between cognitive dysfunction and cortisol alterations might in part reflect independent associations of these variables with either depressive symptoms or sleep problems (early waking). Depressive symptoms were measured with the BDI (Beck and Steer, 1993), a 21-item self-report scale. The BDI item concerning sleep was used to indicate whether a subject had problems with early waking. This item has response categories 0 ‘I sleep as well as before’, 1 ‘I do not sleep as well as before’, 2 ‘In the morning I wake up 1–2 h earlier’, and 3 ‘In the morning I wake up hours earlier and can not fall asleep afterwards’. For data analysis, early waking was categorised as absent (scores 0 and 1), or present (scores 2 and 3). Educational level was indexed on an 8-point scale, ranging from unfinished primary school to university degree (CBS, 1985).

2.4. Data reduction

2.4.1. Cortisol values

Of all 492 cortisol values, four (0.8%) physiologically unlikely high values (>1600 ng/dl), all at 08:00 h, were removed. To avoid bias in cortisol values due to inadequate compliance with the time sampling, samples taken more than 60 min before or after the fixed sample time were deleted from analyses. Over the 2 days, 31 (6.3%) values at 08:00 h, 26 (5.3%) values at 16:00 h, and 27 (5.5%) values at 21:00 h were either outside the acceptable time window or missing. Of these 84 missing values, 27 were from the MDD group, 21 from the AR control group and 36 from the healthy control group. The two cortisol values obtained at the time points on the 2 days were significantly correlated (08:00 h, \( r = 0.40, P = 0.002 \); 16:00 h, \( r = 0.54, P < 0.001 \); 21:00 h, \( r = 0.35, P = 0.006 \)); mean cortisol values for each time point
were, therefore, computed for each subject. When only one cortisol measure was available, this was used as the mean value. In six MDD, five AR, and four healthy individuals, both cortisol values at one of the three time points were sampled out of the time window. In order to include these subjects in the analysis, the missing cortisol values were replaced by the mean cortisol value for each group (Tabachnick and Fidell, 2001). The distributions of all cortisol measures were positively skewed, and natural logarithmic transformations were, therefore, applied prior to analysis to normalise the distributions. The main effect of group on overall cortisol levels was more closely examined by first standardising the cortisol values at each time point over all subjects, and then averaging the three values to obtain a measure of daily average cortisol (DAC) (Gunnar and Vazquez, 2001). The flatness of the cortisol curve over the day was defined as the change in log-transformed cortisol values from 08:00 to 21:00 h (delta cortisol); higher values reflect steeper curves.

2.4.2. Cognitive values

To reduce the number of cognitive measures and the chance of Type I errors due to multiple tests, two compound variables were created: cognitive speed (CST-speed and SCWT-speed) and memory (VVLT-trial 1, VVLT-immediate recall and VVLT-delayed recall). These compound scores were created by first transforming each cognitive value into a normalised $z$-score and then calculating the mean value. The $z$-score for cognitive speed was inverted, so that lower $z$-scores always reflect worse performance. Before analysis, the data were examined for missing values and outliers. Outliers were defined as values with standardised scores in excess of 3.29 ($P < 0.001$), which were disconnected from the other $z$-scores (Tabachnick and Fidell, 2001). Cognitive speed had one outlier, in the healthy control group, which was replaced by the most extreme value within the normal distribution (Tabachnick and Fidell, 2001). There were no missing values.

2.5. Statistical analysis

To test for group differences in cortisol secretory patterns, an analysis of variance (MANCOVA) for repeated measures was performed, with age and sex as covariates. The effect of early awakening on delta cortisol was tested using the dichotomised BDI sleep item as independent variable. Wilks’ Lambda was taken as criterion for significance. Post-hoc univariate testing, adjusted for multiple tests with Scheffé’s test, was used to assess group differences. Group differences in cognitive measures (memory and cognitive speed) were tested using MANCOVA, with age, sex, and education as covariates, and post-hoc comparisons as above. Effects of cortisol (DAC and delta cortisol) on cognition were determined using linear regression. Possible confounding effects of depressive symptoms and group membership were investigated by first entering total BDI score as independent variable in the regression equation, followed by group membership and the two cortisol variables. Two-tailed probabilities of $P \leq 0.05$ were considered significant. Statistical tests were performed with SPSS for Windows version 9.0 (SPSS, Inc., Chicago).
3. Results

3.1. Descriptive data

A total of 27 MDD outpatients, 20 AR controls, and 35 healthy controls were included in the study. Descriptive data on age, sex, education, smoking status, and depressive symptom scores (BDI) are shown in Table 1. There were no differences in age, sex distribution, or smoking status, but the three groups differed significantly in education, with the MDD group having a lower educational level than the AR group. As expected, the MDD group had significantly more depressive symptoms than either control group, whereas the two control groups did not significantly differ in this respect.

3.2. Group differences in cortisol

Fig. 1 shows untransformed cortisol values (ng/dl) for all groups. MANCOVA with repeated measures for cortisol at the three time points (08:00, 16:00, and 21:00 h) adjusted for age and sex, showed a significant main effect of time \((F(2, 77) = 9.089; P < 0.001)\) and an interaction effect of group on time \((F(4, 154) = 3.198; P = 0.015)\). This indicates that a group difference existed in cortisol secretion on one or more of the time points. Post-hoc analyses showed that the MDD group had significantly elevated evening cortisol values compared with the healthy control group \((F(2, 80) = 5.212, P = 0.007)\).

Values for the derived variables DAC (the mean of the three standardised cortisol values) and delta cortisol (the change in log-transformed values from 08:00 to 21:00 h) for the three groups are shown in Table 2. MANCOVA adjusted for age and sex showed an effect of group on delta cortisol \((F(2, 78) = 6.631, P = 0.002)\), but not on DAC \((F(2, 78) = 1.488, P = 0.232)\). Univariate tests adjusted for multiple testing showed that the MDD group differed in delta cortisol from the healthy control group, but not from the AR group: the MDD group had lower delta cortisol (a flatter curve). The flatter cortisol curve of the MDD group was related to significantly elevated evening cortisol values and to non-significantly elevated depression scores.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>MDD (N = 27)</th>
<th>AR (N = 20)</th>
<th>Healthy (N = 36)</th>
<th>Test value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ±S.D.)</td>
<td>41.8 ± 12.7</td>
<td>41.8 ± 10.7</td>
<td>44.6 ± 11.9</td>
<td>(F(2, 80) = 0.59)</td>
<td>0.555</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>44.4%</td>
<td>35.0%</td>
<td>55.6%</td>
<td>(\chi^2 = 2.29)</td>
<td>0.319</td>
</tr>
<tr>
<td>Education (mean ±S.D.)</td>
<td>3.3 ± 1.3</td>
<td>4.6 ± 1.3</td>
<td>4.0 ± 1.7</td>
<td>(F(2, 80) = 4.71)</td>
<td>0.012</td>
</tr>
<tr>
<td>Smoking (% yes)</td>
<td>37.0%</td>
<td>30.0%</td>
<td>16.7%</td>
<td>(\chi^2 = 3.452)</td>
<td>0.178</td>
</tr>
<tr>
<td>BDI (mean ±S.D.)</td>
<td>25.6 ± 9.2</td>
<td>5.2 ± 3.1</td>
<td>3.8 ± 2.8</td>
<td>(F(2, 80) = 126.02)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; AR, allergic rhinitis.
1.543, \( P = 0.220 \) lower morning cortisol values compared with the healthy control group. Since sleep loss can result in altered cortisol levels (especially in evening levels), the effect of habitual early waking on delta cortisol was tested by adding the dichotomised BDI sleep item (presence or absence of early waking problems) to the MANCOVA model. Group differences in delta cortisol remained significant (\( F(2, 77) = 5.202, P = 0.008 \)).

Fig. 1. Untransformed basal cortisol values (ng/dl) for morning, afternoon, and evening samples. Boxes show the median and interquartile range for each group (MDD, major depressive disorder; AR, allergic rhinitis), with whiskers extending from the 10th to the 90th percentile.

<table>
<thead>
<tr>
<th></th>
<th>MDD (( N = 27 ))</th>
<th>AR (( N = 20 ))</th>
<th>Healthy (( N = 36 ))</th>
<th>Test value</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAC (mean ( \pm ) S.D.)</td>
<td>0.17 ( \pm ) 0.66</td>
<td>0.12 ( \pm ) 0.64</td>
<td>0.07 ( \pm ) 0.56</td>
<td>( F(2, 78) = 1.488 )</td>
<td>0.232</td>
</tr>
<tr>
<td>Delta cortisol (mean ( \pm ) S.D.)</td>
<td>1.59 ( \pm ) 0.93</td>
<td>2.06 ( \pm ) 0.71</td>
<td>2.31 ( \pm ) 0.64</td>
<td>( F(2, 78) = 6.631 )</td>
<td>0.002</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; AR, allergic rhinitis.

\(^{a}\) DAC is derived from the cortisol values at 08:00, 16:00, and 21:00 h; the values for each time of day were first standardised over all subjects and then averaged.

\(^{b}\) Delta cortisol is the change in log-transformed cortisol values from 08:00 to 21:00 h.
3.3. Group differences in cognition

MANCOVA showed a significant omnibus-effect of group on the dependent cognitive variables \((F(4, 152) = 2.931, P = 0.023)\). Univariate analysis showed an effect of group on speed \((F(2, 77) = 4.65, P = 0.012)\), but not on memory \((F(2, 77) = 1.80, P = 0.172)\). The MDD group had significantly poorer performance on cognitive speed compared with both the AR group and the healthy group. AR and healthy groups did not differ from each other in cognitive speed. Table 3 shows z-scores (mean and standard deviation (S.D.)) of cognitive speed and memory performance for all groups; Table 4 shows means and S.D.s of the raw cognitive scores.

3.4. Association between cortisol and cognition

Separate linear regression analyses were performed to investigate possible effects of cortisol measures (DAC and delta cortisol) on cognitive speed and memory performance, after controlling for age, sex, and education. Over all subjects, DAC was not related to performance on either speed or memory. No associations between memory performance and delta cortisol were found, but reduced cognitive speed was associated with lower delta cortisol (flatter diurnal curve) \((B = 0.236, t = 2.291, P = 0.025)\) (Table 5). The association between delta cortisol and cognitive speed might be explained by our finding that delta cortisol and cognitive speed both were strongly related to depression. When the analysis was controlled for depression severity (BDI total score) and trichotomous group membership the relation between delta cortisol and cognitive speed was no longer significant \((B = 0.135, t = 1.231, P = 0.222)\). The results indicate that a flatter diurnal cortisol curve and reduced cognitive speed are probably not causally related to each other, but that both vary as a function of the severity of depressive symptoms.

4. Discussion

We investigated basal cortisol levels over the day in relation to cognitive performance (cognitive speed and memory) in young to middle-aged MDD outpatients, with the following specific questions: (1) do these unmedicated MDD outpatients have elevated cortisol levels over the day? (2) Is cortisol related to deficits

Table 3
Z-scores for cognitive speed and memory: mean and standard deviations

<table>
<thead>
<tr>
<th></th>
<th>MDD (N = 27) (mean±S.D.)</th>
<th>AR (N = 20) (mean±S.D.)</th>
<th>Healthy (N = 36) (mean±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive speed</td>
<td>-0.44±1.10</td>
<td>0.30±0.68</td>
<td>0.12±0.61</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.37±0.78</td>
<td>-0.13±0.92</td>
<td>0.11±0.89</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; AR, allergic rhinitis.
in cognitive speed and memory? (3) Are changes in cortisol and cognitive functioning specific to MDD?

Results showed that the MDD group was not characterised by an overall increase or decrease in cortisol levels, but instead by a flattening of the cortisol curve over the day, compared with the healthy control group. This flattening appeared to be mainly due to significantly higher cortisol value in the evening, but non-significantly lower morning cortisol levels were present as well. Higher levels of evening cortisol are not only a feature of hypercortisolemia in older depressive patients (McAllister-Williams et al., 1998; Mitchell, 1995), but have also been reported in adolescents with major depression (Goodyer et al., 1996) and may be a more general characteristic of MDD. Although the possibility of flatter basal cortisol curves over the day has received far less attention than have absolute values of cortisol at specific time points over the day, some recent studies have reported this phenomenon in depression (Deuschle et al., 1997; Gunnar and Vazquez, 2001). One possible explanation for the flatter cortisol curve is early morning awakening, which is often reported by depressive patients. Cortisol secretion follows a diurnal pattern with high levels in the early morning, followed by a decrease over the day, with the trough of the curve in the late

<table>
<thead>
<tr>
<th></th>
<th>MDD (N = 27) (mean ± S.D.)</th>
<th>AR (N = 20) (mean ± S.D.)</th>
<th>Healthy (N = 36) (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST-speed</td>
<td>15.59 ± 5.86</td>
<td>12.50 ± 3.23</td>
<td>13.69 ± 4.23</td>
</tr>
<tr>
<td>SCWT-speed</td>
<td>54.67 ± 9.91</td>
<td>47.31 ± 8.01</td>
<td>49.06 ± 8.41</td>
</tr>
<tr>
<td>VVLT-trial 1</td>
<td>4.44 ± 1.58</td>
<td>4.90 ± 1.65</td>
<td>5.53 ± 1.77</td>
</tr>
<tr>
<td>VVLT-immediate recall</td>
<td>41.63 ± 8.72</td>
<td>44.90 ± 9.32</td>
<td>46.75 ± 9.05</td>
</tr>
<tr>
<td>VVLT-delayed recall</td>
<td>8.70 ± 2.70</td>
<td>9.05 ± 3.10</td>
<td>9.53 ± 2.74</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; AR, allergic rhinitis; CST, Concept Shifting Task; SCWT, Stroop-Colour-Word Test; VVLT, Visual Verbal Learning Test.

<table>
<thead>
<tr>
<th>Overall group</th>
<th>B</th>
<th>Test value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAC on speed</td>
<td>-0.110</td>
<td>-0.182</td>
<td>0.436</td>
</tr>
<tr>
<td>DAC on memory</td>
<td>0.131</td>
<td>0.941</td>
<td>0.350</td>
</tr>
<tr>
<td>Delta on speed</td>
<td>0.236</td>
<td>2.291</td>
<td>0.025</td>
</tr>
<tr>
<td>Delta on memory</td>
<td>0.033</td>
<td>0.315</td>
<td>0.754</td>
</tr>
</tbody>
</table>

a DAC is derived from the cortisol values at 08:00, 16:00, and 21:00 h; the values for each time of day were first standardised over all subjects and then averaged.

b Delta cortisol is the change in log-transformed cortisol values from 08:00 to 21:00 h.
evening (Weitzman et al., 1971). The peak of cortisol secretion occurs approximately 30 min after awakening (Born et al., 1999). In this study, cortisol was measured at a fixed time in the morning (08:00 h), without reference to awakening time (which was not recorded). If MDD subjects woke substantially earlier, on average, than healthy and AR control subjects, their morning peak in cortisol secretion would have occurred well before the 08:00 h sample. If they were mainly due to lower morning cortisol values, the flatter cortisol curves in the MDD group might, therefore, be an artefact. Two findings argue against this explanation: firstly, self-reported early habitual awakening was not significantly associated with cortisol levels. Secondly, the flatter curves appeared to reflect high evening cortisol more strongly than low morning cortisol. However, the fact that awakening time was not recorded and that self-reported early habitual awakening was measured with only one item, represent limitations of this study. Results should be replicated using morning cortisol samples with appropriate control for time since awakening. Furthermore, more precise measures of the sleep pattern, especially in the nights before cortisol sampling, would be very informative.

With respect to cognitive functioning, results showed significant differences in cognitive performance among the groups, but only in cognitive speed: the depressive group showed significant decrements on this measure in comparison to both control groups. This finding is consistent with studies in geriatric depressive patients (Beats et al., 1996; Nebes et al., 2000; Videbech, 2000) and in younger depressive patients (Tsourtos et al., 2002). Surprisingly, memory performance did not differ among the three groups. However, although memory deficits have consistently been reported in older depressive patients (Austin et al., 2001; Burt et al., 1995) as well as in younger psychotic depressive patients (Schatzberg et al., 2000), results for younger non-psychotic depressive patients have been mixed, with some negative findings (Grant et al., 2001; Purcell et al., 1997). Current theories of cognitive ageing may help explain why memory deficits are less likely to be observed in younger MDD patients. Salthouse and colleagues (Kail and Salthouse, 1994; Salthouse, 1996) have argued that speed of information processing should be considered a resource for cognitive functioning. According to them, slower information processing may affect higher information processing, for example because end products of basic processing are sometimes no longer accessible when they are needed for higher cognitive processing. This mechanism may apply to depressive disorder as well. Whether or not higher cognitive functioning such as memory is affected may depend on several factors, such as the degree of impairment in information processing speed and the degree to which individuals are able to compensate. It is possible that younger outpatients are better able to compensate for reduced cognitive speed than older or more severely depressed patients. Accordingly, deficits in higher cognitive functioning (like memory) may not manifest themselves in younger depressive outpatients.

With respect to the relationship between cortisol and cognitive functioning, it is noteworthy that over all subjects, increasing flatness of the cortisol curve was associated with reduced cognitive speed. This finding is in line with the idea that cortisol may affect areas in the brain besides the hippocampus, notably the frontal
lobe, since glucocorticoid receptors are abundant in that area (Neylan et al., 2001; McCormick et al., 1995; Lupien et al., 1999). The frontal lobe comprises specific cognitive functions, notably working memory, executive function, and cognitive speed. As described above, cognitive speed is sometimes characterised as a fundamental part of the architecture of cognitive functions (Kail and Salthouse, 1994), or a resource for cognitive functioning (Salthouse, 1996). Deficits in cognitive speed may, therefore, be an early sign of diminished cognitive performance. This may explain the association between a flatter cortisol curve and cognitive speed. However, when depressive symptoms and group membership were controlled for in this study, this association was not present any more. This suggests that a flatter diurnal cortisol curve is actually not causally related to reduced cognitive speed, but that both a flatter diurnal cortisol curve and reduced cognitive speed are influenced by depressive symptoms.

Finally, we investigated the specificity of changes in cortisol and cognitive functioning for MDD. The depressive group differed on flatness of cortisol curve from the healthy group, but not from the AR group. This suggests that a flatter diurnal cortisol curve is not specific for depressive disorder. This is in line with findings from Smyth et al. (1997) and Stone et al. (2001), who reported that 10–17% of healthy people do not show a diurnal cycle. With respect to cognitive function, the deficit in cognitive speed was specific for the MDD group, which makes it unlikely that this impairment is caused by more general secondary disease-related factors.

A limitation of the study is that in the depressed patients, the total time being depressed was not recorded. This variable may be of influence on cortisol secretion and cognitive functioning. However, in the present study no patient had an excessive long period of depressive disorder before admittance to the clinic. Nonetheless, it would be wise to include a measure of total time depressed in future research.

In summary, young to middle-aged unmedicated outpatients with MDD, compared with healthy individuals and AR outpatients, showed reduced cognitive speed. Compared with the healthy controls, the MDD patients showed a flatter cortisol curve over the day, with significantly higher cortisol levels in the late evening. We found no clear evidence that the observed association between a flatter cortisol curve and reduced cognitive speed was causal; instead, both abnormalities appear to reflect the severity of depressive symptoms.

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