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ORIGINAL PAPER

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Neuropsychological and hypothalamic–pituitary-axis function in female patients with melancholic and non-melancholic depression

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Abstract *Background* Executive function deficits in depression implicate involvement of frontal–striatal circuits. However, studies of hypothalamic–pituitary-axis (HPA) function suggest that stress-related brain changes of hippocampus may also implicate prefrontal–hippocampal circuits, which may explain the profile of both executive dysfunction and memory deficits. In this study we examined the performance of patients with major depressive disorder (MDD) on tasks of memory and executive function in relation to melancholic features and to cortisol levels. Our hypothesis was that raised cortisol levels in melancholic patients would correlate with these deficits. *Method* Forty female MDD patients, 20 having melancholic features (MEL vs. Non-MEL), and 20 sex- age- and education-matched normal controls were investigated using the Cambridge neuropsychological test automated battery (CANTAB), to assess memory (paired associative learning, PAL; short-term recognition memory, SRM) and executive (intradimensional/ extradimensional set-shifting, ID/ED; Stockings of Cambridge, SOC) functions. Plasma and salivary cortisol levels were measured. *Results* The MDD patients performed worse than controls on PAL and both executive tasks. The MEL group differed from controls on all tests, and differed from the non-MEL only at the ED stage of the ID/ED task. Patient cortisol levels were within the normal range and did not correlate with neuropsychological performance for any group. *Conclusions* MDD patients showed neuropsychological deficits on tasks of executive function and memory, supporting the model of frontal-temporal dysfunction. MEL vs. non-MEL performed worse overall and demonstrated a qualitative difference in set shifting, perhaps implicating more extensive prefrontal involvement. Cortisol levels did not correlate with depression severity or the observed deficits.

Key words Cambridge Neuropsychological Test Automated Battery (CANTAB) · cortisol · depression · melancholic features · set shifting

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Introduction

In recent years the exploration of neuropsychological deficits in depression has attracted increasing experimental interest. The degree of cognitive deterioration appears to vary across individuals: in some patients such deterioration is barely discernible, while in others, especially elderly patients, it is pronounced enough to warrant a differential diagnosis for dementia ("reversible dementia" or "pseudodementia") [1]. Even in mild cases, cognitive deterioration interferes with the patient's efforts to regain premorbid levels of functioning and return to normal living conditions. The corpus of relevant findings to date appears to support the hypothesis of a dysfunction in fronto-striatal circuits [2].

One of the most consistent findings reported by studies focusing on the neuropsychology of depression is an executive deficit in depressive patients compared to control subjects [2–7]. Studies on aged depressive patients have established deficits in visuospatial memory as well as in executive functions such as attentional set shifting, planning and problem solving [8–10]. Interestingly, similar deficits have been reported by studies on younger patients [11–13] and have been correlated with number of previous hospitalizations, an index of disease severity [11]. Neuroimaging studies have produced compatible findings. Specifically, both fMRI [14, 15] and PET [16] studies have demonstrated dysfunction in prefrontal–striatal regions in depressed patients. In the study of Elliott et al. [17], patients with middle-range severity of depression, presented memory and planning deficits but performed similarly to normal in set-shifting. In contrast, a study comparing depressed patients to patients with obsessive compulsive disorder (OCD) and panic disorder, confirmed the pattern of set-shifting deficits in the depressed group [18]. Cognitive deficits in major depressive disorder (MDD) appear to be trait rather than state markers, as they are discernible not only during active depression but also in remission periods [19–21]. Corresponding findings have been reported in aged depressive patients [22]. The memory deficits in depression, a finding shared by several studies [23], have been attributed to hippocampal dysfunction [24, 25], possibly due to cortisol neurotoxicity. Increased cortisol levels have been associated with depression on the basis of animal experiments [26] as well as clinical studies which indicate increased concentrations in specific brain areas, particularly hippocampus [27] and prefrontal cortex [28]. Nevertheless, there are reports which do not corroborate the hypercortisolaemia hypothesis [29] in which free plasma or urine cortisol levels appear to correlate neither with memory deficits nor with hippocampal volume [30]. These findings are at odds with the hypothesis of cortisol neurotoxicity affecting the hippocampal formation [31].

With respect to neuropsychological differentiation between different depression subtypes, the available data are limited. Consistent findings suggest dysfunction of the frontal and temporal lobes in patients with psychotic depression [32, 33]. Furthermore, patients with melancholic depression demonstrate psychomotor retardation and executive dysfunction compared with depressed patients without melancholic features [6, 34, 35]. Similar findings were reported in a study which compared a depressed patient group with predominant psychological symptoms to a depressed group with predominant vegetative symptoms [36].

The present study used computerized, non-verbal testing procedures from Cambridge Neuropsychological Test Automated Battery (CANTAB) [37, 38] to investigate memory and executive functions of depressed patients with and without melancholic features. The neuropsychological performance of these two patient groups was compared to that of age- and education- matched healthy controls. Following this, performance of the patient groups was correlated with morning and 24-h plasma and salivary cortisol levels.

Materials and methods

Patients

The study sample consisted of 40 female patients and 20 age and education-matched controls. All participants were either recently admitted to a female short-stay or were being evaluated for admission by the Women's Mental Health Clinic at Eginition Hospital, Athens University Medical School. In addition to patient availability, however, we decided that the restriction of our sample to women would serve an additional purpose. Depression in women is more frequent than in men [39, 40] and neuropsychological function differences have been reported between males and females [41, 42]. Therefore an all—female sample could enhance homogeneity in our investigation. All patients met criteria for major depressive disorder (MDD) according to DSM-IV-TR [43].

All patients underwent a structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders) [44], before admission to the study. During the diagnostic interview patients with MDD were placed in one of two categories according to the presence or absence of melancholic features in the clinical picture, as assessed by DSM-IV-TR [43] criteria: 20 had depression with melancholic features (MEL) and 20 had depression without melancholic features (non-MEL).

Patients with a history of any other major psychiatric disorder such as schizophrenia, schizoaffective disorder, delusional or bipolar disorder as well as those presenting MDD with psychotic features were excluded. Additionally, patients suffering from central nervous system disorders such as dementia, Parkinson's disease, epilepsy, brain tumors or an established organic brain syndrome, or with a history of cerebrovascular episodes, serious endocrine conditions or malignancies, as well as cases of substance abuse or dependence from alcohol, sedative or hypnotic substances were also excluded. All patients were under pharmacotherapy but patients who had undergone electroconvulsive therapy (ECT) in the last 5 years were excluded. Twenty controls matched for sex, age and education were also included. They were selected from a sample of medical patients undergoing screening for hepatitis CV or from the hospital staff. Inclusion criteria for controls: willingness to participate and absence of psychiatric disturbance in the past or in the mental status examination. Exclusion criteria for controls were the same as for the patients.

The patients' and controls cognitive functions were screened by the Mini Mental State Examination (MMSE) [45]. The 17-item Hamilton Rating Scale of Depression (HAM-D) was used to estimate the severity of depression. The score of 17 was used as inclusion criterion [46].

Procedure

Between 4 and 8 days post-admission or within a week from the diagnostic interview all patients were subjected to:

(a) Blood test to assess morning cortisol levels (CORT).
(b) Salivary test to assess cortisol levels (three daily samples: morning, 08.00 a.m. [CS1]; noon, 16.00 p.m. [CS2] and night, 23.00 p.m. [CS3]). Salivary cortisol level detection was carried

out by enzyme immunoassay (ELISA), a reliable method used in previous studies [47–49]. Saliva samples were tested for blood contamination by enzyme immunoassay and samples with transferrin values greater than 1 mg/dl were excluded [50–52].

(c) Neuropsychological assessment by means of a selection of subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). For all patients CANTAB assessment was administered in the middle of the day (13.00–17.00), to control for diurnal variation of cognitive function depending on depression type and cortisol levels [53, 54].

CANTAB executive function tasks

1. Stockings of Cambridge Task (SOC) assesses the subject's ability to rearrange a set of balls in a specified minimum number of moves and minimum time. The subject is directed to plan the sequence of moves before the initiation of movement.
2. Intradimensional/extradimensional (ID/ED) attentional set shifting task assesses the subject's ability to maintain attention to different examples within a stimulus dimension (intradimensional shift) and to then shift attention to a previously irrelevant stimulus dimension (extradimensional shift). The subject proceeds to nine stages and performance was assessed as the number of stages completed and the number of errors made before and during the extradimensional shift.

CANTAB visual memory tasks

1. Spatial recognition memory task (SRM) assesses the subject's ability to recognize the correct spatial location of a square presented on five occasions sequentially at different locations on the screen, followed by a paired series of novel and previously shown squares.
2. Paired associates learning task (PAL) assesses the subject's ability to learn associations between designs and their locations on the screen. Subjects have to indicate the square in which every design was previously presented, starting with one design among six squares and ending with eight designs among eight squares.

Statistical analysis

Statistical analysis was carried out using SPSS (Version 11.0) for Windows. The following tests were used for the statistical analysis of the data: The Pearson χ^2 test for comparison of percentages, t test and one-way ANOVA (with Bonferroni correction) for comparison of means of variables presenting normal distribution, and Mann–Whitney U tests and Kruskal–Wallis non-parametric analysis of variance for variables which were not normally distributed. Multiple regression analysis was used to examine the affect of medication on the CANTAB tasks. Correlations were tested by the Pearson r or the Spearman rho coefficient, depending on whether the variables were normally distributed or not. Latencies in Stockings of Cambridge Task were transformed into logarithms to reduce skewness in the distribution.

Results

Sample characteristics

As mentioned, the sample (40 patients and 20 controls) consisted exclusively of women. The mean age was 51.7 ± 11.4 years. The mean length of education was 11.2 ± 4.2 years. 23 of the 60 women examined were pre-menopausal and were menstruating regularly, five were perimenopausal and 32 were post-menopausal.

The mean age for the depression group was 52.7 ± 10.8 years, while the controls had a mean age of 49.8 ± 12.7 years. Depressed patients had a mean length of education of 10.8 ± 4.2 years, controls 12.1 ± 4.0 years. The mean age of onset of the disorder was 36.4 ± 10.7 years; the mean duration of the disorder was 16.2 ± 9.5 years. The mean score of number of episodes was 6.4 ± 5.2 and the mean number of hospital admissions was 2.0 ± 2.2. The mean score for the MMSE was 28.8 ± 1.4 and the HAM-D 20.0 ± 4.0.

All patients were receiving pharmacotherapy at the time of testing: 22 were treated with specific serotonin reuptake inhibitors (SSRIs), 16 were on serotonin and noradrenaline reuptake inhibitors (SNRIs) or mirtazapine, 14 were receiving tricyclic antidepressants, six on lithium, and eight on anticonvulsants. Thirty-one women were receiving benzodiazepines, 15 on atypical antipsychotics and eight were receiving thyroxine supplementation.

Comparisons

Patients and controls did not differ in age ($t = 0.93$, $P = 0.35$ t test) and years of education ($z = -1.09$, $P = 0.27$ Mann–Whitney U test). Additionally, they did not differ in menstruation or menopause status ($\chi^2 = 0.85$, $P = 0.6$ Fisher's exact test). No difference was observed when the controls were compared to patients with MEL and non-MEL for age ($F = 1.34$, $P = 0.26$ ANOVA), as well as years of education ($P = 0.51$ Kruskal–Wallis test). The two clinical groups and the control group were also comparable in terms of menstrual stage ($\chi^2 = 6.68$, $P = 0.13$, Fisher's exact test). The comparison of demographic and clinical features of the MEL and non-MEL groups did not produce any statistically significant differences (Table 1). Further, the two patient groups did not differ in any of the pharmacotherapy categories compared using the Fisher's exact test (for SSRIs $P = 0.75$, SNRIs $P = 1.00$, tricyclics $P = 1.00$, lithium $P = 1.00$, anticonvulsants $P = 0.23$, antipsychotics $P = 0.51$, benzodiazepines $P = 1.00$, thyrormone $P = 0.69$). In order to examine the impact of medication on neuropsychological tasks we grouped the medication in "sedatives" or "non-sedatives" (SSRIs and SNRIs vs. mirtazapine, tricyclics, antipsychotics and mood stabilizers); there was no difference between MEL and non-MEL ($\chi^2 = 0.4$, $P = 0.751$). Multiple regression analyses were performed (dependent variable: task score, independent variables: melancholia, sedatives) showing that "sedatives" did not affect the cognitive task scores.

Table 1 Demographic and clinical characteristics of patients

	Melancholics	Non-melancholics	Test	*P*
Age	55.1 ± 10.1	50.3 ± 11.1	$t = -1.43$	0.15
Education (years)	11.0 ± 4.4	10.6 ± 4.1	$z = -0.34$	0.75
MMSE	28.5 ± 1.5	29.1 ± 1.3	$z = -1.64$	0.10
HAM-D	20.2 ± 3.2	19.8 ± 4.8	$t = -0.86$	0.39
Illness age of onset (years)	37.9 ± 8.6	34.9 ± 12.5	$z = -1.09$	0.27
Illness duration (years)	17.1 ± 10.5	15.4 ± 8.7	$z = -0.28$	0.77
Number of episodes	6.1 ± 4.9	6.8 ± 5.5	$z = -0.14$	0.90
Number of hospitalizations	1.7 ± 2.0	2.2 ± 2.5	$z = -1.13$	0.28

MMSE Mini mental state examination, *HAM-D* Hamilton rating scale for depression, *t* *t* test, *z* Mann–Whitney *U* test, *SD* standard deviation, *P* sig

Cortisol

For the depressed patients, the mean value of plasma cortisol (morning reading) was 19.3 ± 6.8 μg/dl, while the mean values of salivary cortisol were: morning (CS1) = 0.42 ± 0.34 ig/dl, noon (CS2) = 0.15 ± 0.11 ig/dl and night (CS3) = 0.08 ± 0.10 ig/dl. Comparison of cortisol values of the two depressed patient groups indicated that the MEL group had generally higher cortisol values. However, this difference did not reach statistical significance (Table 2).

Table 2 Comparison of cortisol samples between melancholics and non-melancholics

	Melancholics	Non-melancholics	Test	*P*
Cortisol (blood) (mg/dl)	19.52 ± 8.05	19.11 ± 5.78	$t = -0.18$	0.85
Saliva cortisol morning (ig/dl)	0.49 ± 0.35	0.35 ± 0.33	$z = 0.14$	0.15
Saliva cortisol noon (ig/dl)	0.16 ± 0.12	0.15 ± 0.11	$z = -0.06$	0.95
Saliva cortisol night (ig/dl)	0.08 ± 0.06	0.08 ± 0.12	$z = -0.25$	0.80

t *t* test, *z* Mann–Whitney *U* test, *SD* standard deviation, *P* sig

Neuropsychological assessment

Comparison of depressed patients and controls

MDD patients generally performed worse than controls on CANTAB tests. On the SRM task the difference was not statistically significant. However, MDD patients made significantly more errors than controls in the PAL task ($P = 0.001$). They also made significantly more overall errors on the ID/ED task ($P = 0.049$). When the number of errors was adjusted in relation to the successful stages, the difference between MDD patients and controls remained significant ($P = 0.041$). On the SOC task MDD patients solved fewer problems within the fewest possible movements ($P = 0.01$). They did not differ from controls in the time taken to plan and initiate problem solving ($P = 0.77$), although they did differ in the thinking time taken to solve 5-move problems after initiation ($P = 0.04$) (Table 3).

Comparison of melancholic and non-melancholic patients with controls

Most of the performance differences noted between MDD patients and controls were sustained when MDD patients were subdivided into MEL and non-MEL groups. The three-group comparison showed significant difference on SRM scores ($P = 0.036$), on the PAL ($P = 0.002$) and the ID/ED task. In the latter, differences were significant both in the number of stages successfully completed ($P < 0.001$) and in the number of errors ($P = 0.05$ for overall errors, $P = 0.001$ for number of errors adjusted; five MEL patients were excluded from the analysis because they could not proceed beyond the second stage of the task). On the SOC task, a significant difference was noted only in the number of problems solved in the fewest possible movements ($P = 0.03$), whereas there was no difference in times (Table 4).

Post hoc analyses revealed that: MEL patients performed significantly worse on all the tasks compared to controls. Non-MEL patients performed worse than controls only on the PAL task ($P = 0.03$), and there were no differences on any other task. MEL patients' scores were not statistically significant from Non-MEL patients on the PAL, SRM and SOC tasks. However, differences were found on the ID/ED task: MEL did not show differences in the total errors ($P = 0.15$), but differences were found when the

Table 3 Neurocognitive profile of patients and controls

	Depressed	Controls	Test	*P*
PAL Total errors	66.3 ± 44.5	32.5 ± 36.3	z = −3.22	**0.001**
SRM Correct (%)	63.9 ± 14.3	70.7 ± 14.5	z = −1.36	0.17
ID/ED Stages completed	8.4 ± 0.8	8.8 ± 0.4	z = −2.00	0.06
ID/ED Total errors	27.4 ± 17.5	18.1 ± 10.3	z = −2.00	**0.049**
ID/ED Adjusted errors	33.8 ± 13.2	19.4 ± 13.2	z = −2.16	**0.041**
SOC Problems solved in minimum moves	6.1 ± 2.0	7.6 ± 1.9	t = −2.59	**0.01**
Log SOC in mean initial thinking time (five moves)	8.7 ± 1.2	8.7 ± 0.4	z = −0.28	0.77
Log SOC sub mean subsequent thinking time (five moves)	7.8 ± 1.4	7.2 ± 1.0	z = −2.05	**0.04**

PAL Paired associates learning task, *SRM* spatial recognition memory task, *ID/ED* intradimensional/extradimensional attentional set shifting task, *SOC* stockings of Cambridge task, *t* *t* test, *z* Mann–Whitney *U* test, *SD* standard deviation, *P* sig

Table 4 CANTAB comparisons for the two patient groups and controls

	Melancholics	Non-Melancholics	Controls	Test	*P*
PAL Total errors	78.9 ± 42.8	54.3 ± 43.7	32.5 ± 36.3	KW	0.002
SRM Correct (%)	59.1 ± 17.0	68.2 ± 9.9	70.7 ± 14.5	*F* = 3.52	0.036
ID/ED Stages completed	7.8 ± 0.9	8.8 ± 0.4	8.8 ± 0.4	KW	<0.001
ID/ED Total errors	32.9 ± 20.1	23.2 ± 14.4	18.1 ± 10.3	KW	0.05
ID/ED Adjusted errors	46.2 ± 27.7	24.5 ± 17.3	19.4 ± 13.2	KW	0.001
SOC Problems solved in minimum moves	5.8 ± 2.0	6.3 ± 2.0	7.6 ± 1.9	*F* = 3.54	0.03
Log SOC in mean initial thinking time (five moves)	8.6 ± 1.7	8.8 ± 0.8	8.7 ± 0.4	KW	0.75
Log SOC sub mean subsequent thinking time (five moves)	8.1 ± 1.1	7.6 ± 1.5	7.2 ± 1.0	KW	0.11

PAL Paired associates learning task, *SRM* spatial recognition memory task, *ID/ED* intradimensional/extradimensional attentional set shifting task, *SOC* stockings of Cambridge task, *SD* standard deviation, *KW* Kruskal–Wallis test, *F* one way ANOVA (Bonferroni correction), *P* sig

Table 5 CANTAB comparisons for the three groups per two

	Melancholics vs. non-melancholics	Melancholics vs. controls	Non-melancholics vs. controls
PAL Total errors	0.08	<0.001***	0.03*
SRM Correct (%)[1]	0.15	0.04*	1.00
ID/ED Stages completed	0.008**	0.008**	1.00
ID/ED Total errors	0.15	0.016*	0.27
ID/ED Adjusted errors[a]	0.006**	0.001**	1.00
SOC Problems solved in minimum moves[a]	1.00	0.04*	0.17

PAL Paired associates learning task, *SRM* spatial recognition memory task, *ID/ED* intradimensional/extradimensional attentional set shifting task, *SOC* stockings of Cambridge task

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

[a]ANOVA (Bonferroni correction), others: Mann–Whitney *U* test

number of errors was corrected in relation to the successful stages ($P = 0.006$), with MEL patients completing fewer stages on the task ($P = 0.008$). The MEL patients were significantly more likely to fail at the Extradimensional shift stage ($\chi^2 = 12.0$, $P = 0.001$, Fisher's exact test). It should be noted that at this stage non-MEL did not differ from controls (Table 5).

Correlations

Significant correlations between the CANTAB tasks and clinical measures were as follows: The PAL task (number of errors) was associated with age ($r = 0.59$ $P < 0.001$), years of education ($r = -0.50$; $P < 0.001$), duration of the disorder ($r = 0.42$; $P = 0.008$), number of episodes ($r = 0.33$; $P = 0.04$), number of hospital admissions ($r = 0.36$; $P = 0.02$) and MMSE ($r = -0.64$; $P < 0.001$). The SRM task (percentage of correct answers) was correlated with age ($r = -0.30$; $P = 0.01$), years of education ($r = 0.27$; $P = 0.03$) and the MMSE ($r = 0.34$; $P = 0.03$). Total errors on the ID/ED task was correlated with the morning salivary cortisol level ($r = 0.36$; $P = 0.03$), and the number of adjusted errors on ID/ED was associated with age ($r = 0.27$; $P = 0.04$). The number of problems solved on the SOC task ($r = -0.42$; $P = 0.002$) as well as the time for movements after beginning the task (log-SOCsub) ($r = 0.32$; $P = 0.02$) were correlated with age.

There were also no significant correlations between cognitive performance and depression severity (HAM-D score): (ID/ED stages: $r = -0.198$; $P = 0.247$, ID/ED total errors: $r = 0.129$; $P = 0.455$, ID/ED errors adjusted: $r = 0.174$; $P = 0.311$, PAL: $r = 0.310$; $P = 0.062$, SRM: $r = 0.073$; $P = 0.662$, SOC problems $r = 0.157$; $P = 0.382$, SOC initial time $r = 0.061$; $P = 0.755$, SOC subs time $r = -0.153$; $P = 0.436$).

All cortisol values, apart from the one mentioned above, showed correlations between different samples, as was expected: The morning salivary cortisol value was correlated with the morning plasma cortisol value ($r = 0.55$; $P = 0.001$) and the midday salivary cortisol level was correlated with the evening salivary cortisol level ($r = 0.42$; $P = 0.01$). It is important to report that the association between morning salivary cortisol and the ID/ED total errors ($r = 0.363$; $P = 0.038$) was the only significant correlation between cortisol values and CANTAB tests, either mnemonic or prefrontal. The other associations appear in Table 6.

When the patients were divided in MEL and non-MEL, their cortisol values showed significant correlations with some of the CANTAB tests. For MEL: *noon salivary cortisol* with SOC problems ($r = 0.816$; $P = 0.001$). For non-MEL: *cortisol plasma* with ID/ED stages ($r = -0.518$; $P = 0.019$) and SOC problems ($r = -0.517$; $P = 0.028$), *morning salivary cortisol* with ID/ED total errors ($r = 0.633$; $P = 0.004$) and ID/ED adjusted errors ($r = 0.621$; $P = 0.005$).

Discussion

In this study of female patients with MDD, we identified neuropsychological deficits on tasks of executive function and memory. Compared with non-melancholic patients, those with melancholic features performed worse overall and demonstrated a qualitative difference on the attentional set-shifting task of the CANTAB, with impairment evident at the extradimensional shift stage. This suggests that MEL and non-MEL patients differ qualitatively and may rep-

Table 6 Correlations between cortisol values and CANTAB task scores

	Cortisol (blood)	Saliva cortisol morning	Saliva cortisol noon	Saliva cortisol night
ID/ED	−0.274	−0.224	0.141	0.046
Stages completed	0.116	0.209	0.450	0.801
ID/ED	0.140	0.363	0.000	0.259
Total errors	0.431	0.038*	1.00	0.153
ID/ED	0.194	0.281	−0.139	0.108
Errors adjusted	0.272	0.113	0.457	0.555
PAL	0.114	0.073	−0.140	−0.093
Errors	0.513	0.683	0.444	0.606
SRM	0.043	−0.292	−0.019	0.165
Correct (%)	0.801	0.089	0.916	0.351
SOC	−0.294	−0.156	0.304	−0.220
Problems solved	0.103	0.409	0.116	0.251
SOC	0.182	0.361	0.350	0.205
Initial time (log)	0.344	0.070	0.086	0.326
SOC	0.114	0.244	0.004	0.285
Subsequent time (log)	0.564	0.239	0.984	0.177

In the first line of every box: Spearman's coefficient (*r*), in the second line of every box: level of statistical significance (*P*)
* $P < 0.05$, nonparametric correlations

resent different subgroups of depression. There was no evidence to support the hypothesis that melancholic patients would have raised cortisol levels. While an association was found between total errors on the ID/ED task and morning salivary cortisol level, this finding should be treated cautiously as no other significant associations were found.

MDD patients, as a group, showed differences on the associative memory task (PAL), while there was no deficit found in spatial recognition memory (SRM), suggesting that there is a specific impairment in the ability to learn random visuospatial associations. Based on previous studies demonstrating that impaired performance on PAL may serve as a marker for preclinical Alzheimer's disease [55–57], in which hippocampal involvement occurs early, the deficits we identified implicate the involvement of medial temporal lobe structures, particularly the hippocampus [58]. Further, we found an association between performance on PAL and clinical measures of disease severity and chronicity (illness duration, number of episodes and hospital admissions), suggesting that these abnormalities may only become apparent as the illness progresses.

Overall, patients with MDD also showed differences compared to controls for both tasks assessing executive functions, that is, on the ID/ED task (at the ED stage specifically) and the SOC task (fewer problems solved accurately and greater time required to solve problems subsequent to the first move). While there were correlations between these executive functions with age, there were no significant associations with clinical measures of illness severity. These findings are consistent with previous studies [2–7].

When melancholic and non-melancholic groups were considered separately, non-MEL patients showed differences from controls only for visuospatial associative memory and learning (PAL), while MEL patients showed impairments compared with controls on all memory and executive tasks. Further, MEL patients were significantly impaired in comparison with non-MEL patients only at the extradimensional shift stage of the attentional set shifting (ID/ED) task. In contrast, on the SOC task (assessing planning and execution, without set shifting) MEL patients did not differ from non-MEL patients. Similar differences have been reported in the study by Austin et al. [6], although in that study MEL and Non-MEL patients differed significantly for age and HAM-D score making it difficult to assert that these groups were different or merely reflected greater illness severity in the MEL patients. In the present study, MEL and non-MEL did not differ in age, education, MMSE, pharmacotherapy and severity of disease (HAM-D, illness years, number of episodes and hospitalizations), therefore, the observed difference on the ID/ED task could not be explained as a quantitative difference. Rather, our findings provide evidence to support the notion that MEL and non-MEL patients differ qualitatively and represent different subgroups of depression [59]. We found a specific deficit in ED shifting in melancholic patients, while non-melancholics performed identically to normal subjects, with no impairments in reversal learning were apparent in either group. Thus, while the deficits in associative memory were common to both depressive groups, implicating temporal lobe involvement, the executive pattern of deficits suggests a specific involvement of DLPFC in melancholic rather than non-melancholic depressives. In this context, the reported findings from other studies that depressives as a group manifest neuropsychological deficits attributed to DLPFC may be explained by specific deficits that are a feature of the melancholic subtype. Further, while we did not find evidence for impaired OFC function, further studies using more specific tasks relevant to the OFC are required.

Depressive patients showed normal cortisol blood levels and there was no difference between MEL and non-MEL in any of the cortisol samples. MEL showed slightly higher values, especially in the morning salivary cortisol, but this did not reach statistical significance in our sample. There was also no correlation between the cortisol levels and the neuropsychological tests with the exception of a moderate positive correlation between morning salivary cortisol and total ID/ED errors. Furthermore, the non-MEL group showed more correlations between morning cortisol levels and ID/ED task errors. It could be assumed that the positive correlation between morning cortisol levels and ID/ED total errors, which was found for the depressive patients, could be attributed to the impact of the non-MEL

group. These findings do not seem to follow the hypothesis of hypercortisolaemia in depression, especially for the melancholic type, or the cortisol neurotoxicity theory [27, 28, 60, 61]. On the other hand, cortisol levels were not correlated with depression severity (HAM-D), supporting the findings of recent studies in which cortisol levels were dissociated from depression severity in their impact on cognitive function [28, 62]. However, hypercortisolaemia has not been a stable finding in all studies and a dysfunction of the HPA axis has been proposed as an alterrnative hypothesis [29, 63], especially for the depressive patients with melancholic features [64]. In order to extend our investigation to the detection of HPA dysregulation we would need more refined methods [63]. There are also some studies that do not support the neurotoxicity theory: mnemonic deficits and hippocampal volume are correlated but it has proved difficult to identify a relationship to cortisol [30, 31], which may require long-term longitudinal evaluation. The associations of performance on PAL with illness duration and illness episodes are of interest here. PAL has been considered to probe medial temporal (hippocampal) function, which is affected structurally and functionally by the effects of cortisol [65]. Our correlational findings would suggest that this relationship may only be apparent following several illness episodes and duration of the depression may also be relevant. No studies have examined this interaction dynamically over the course of the illness. The assessment of the role of cortisol ideally requires long-term follow-up studies to examine the impact of HPA axis function on neuropsychological function and other brain indices, as a cross-sectional study cannot address the dynamic changes over time.

We consider as limitations of our study the following: All patients were receiving medication during neuropsychological assessment. This could affect their comparison to controls. However, the two patient groups did not differ in medication categories, a fact that might "make up" for this limitation in the MEL vs. non-MEL comparison. Further, our sample consisted of moderate to severe depressed, patients, and all were female. Even though this was done by choice, as mentioned in the method section, our results cannot be readily generalized to other groups, such as male patients, mildly depressed or exclusively geriatric patients; all these patient groups could show different results, and further studies to include these populations should be undertaken. Finally, we have not used verbal tests of cognitive assessment (involving memory and information processing) or other tests examining attention only. However, given the type of illness and its severity, the increased number of tests could confound the performance and question the reliability of the results.

In the present study depressive patients showed neuropsychological deficits in visuospatial memory and executive function. Overall, these deficits showed no correlation with severity of depression or cortisol levels (blood and saliva), which were within normal limits. Our findings support the model of frontal–temporal dysfunction in depression. Further, we demonstrated that compared with non-melancholic patients, well-matched melancholic depressive patients had worse overall neuropsychological function and showed a qualitative difference in set shifting, perhaps implicating more extensive prefrontal involvement, particularly of DLPFC. Longitudinal studies are needed adequately to investigate the role of HPA axis function dynamically, and to assess the contribution of stress and stress-related hormones to the findings of temporal lobe dysfunction in both types of depression.

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