Paper I

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Impairment across executive functions in recurrent major depression

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Depression is associated with impairment of cognitive functions, and especially executive functions (EFs). Despite the fact that most depressed patients experience recurrence of episodes, the pattern and the severity of executive impairment have not been well characterized in this group of depressed patients. We asked if and to what extent these patients were impaired on a range of neuropsychological tests measuring EFs, and also when confounding factors were adjusted for. Forty-five patients (aged 19–51 years) with moderate to severe (Hamilton score >18) recurrent major depressive disorder (DSM-IV) were compared to 50 healthy controls matched on age, education, gender and intellectual abilities. The subjects were administered a set of neuropsychological tests that assesses sub-components of EFs. The depressed patients were impaired compared to the control group on all selected tests, with a severity of impairment within -1 standard deviation from the control group mean. The group difference was statistically significant for eight of the 10 EFs that were assessed. These were measures of verbal fluency, inhibition, working memory, set-maintenance and set-shifting. The group difference was still significant for all sub-components except for set-shifting (Wisconsin Card Sorting Test) and planning (Tower of London), when additional medication and retarded psychomotor speed was adjusted for. In conclusion, the depressed subjects were mildly impaired across a wide range of EFs. This may have a negative impact on everyday functioning for this group of patients.
• *Executive functions, Major depressive disorder, Neuropsychological tests.*

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Major depression is a heterogeneous illness, and the majority of patients experience recurrent episodes and are at high risk of psychosocial impairment and suicide (1).

Cognitive deficits are well documented in neuropsychological studies of patients with major depression on tests of attention (2), memory functions (3), psychomotor functions (4) and executive functions (5–8).

Several studies have indicated that the symptoms and cognitive deficits seen in depression are associated with a neurobiological dysfunction involving frontal–subcortical neuronal circuitries (9–13). Results from functional brain imaging studies (fMRI) have confirmed decreased blood flow and glucose metabolism in the resting state in prefrontal cortex, striatum, pallidum and thalamus (11, 14–16). Cognitive activation studies using positron emission tomography (PET) are less conclusive, but indicate that depression is associated with an activation level in frontal and prefrontal regions that is different from what is found in normal controls (17). Recurrent unipolar major depression has recently been associated with volume loss of the same structures as mentioned above, and hypercortisolemia has been suggested as one possible aetiological mechanism for these structural changes (18).

The frontal cortex is critical for the control of cognitive processes involved in complex intentional behaviour. These processes have been referred to as executive functions (EFs), a controversial concept that is both difficult to define and operationalize (19). Bryan & Luszcz (20) refer to EFs as "cognitive processes that control and integrate other cognitive activities". The concept has been further explained by separating it into several sub-components, i.e. set-shifting, planning, inhibition, working memory and fluency (21). These sub-components have been operationalized by referring to cognitive tests that assess specific components of EF. Some authors have suggested that EF is especially

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affected in patients with depression (9, 22), and that EF seems to be one of the earliest affected cognitive domains in the progression of depression (7).

It is well known that cognitive functions in patients with unipolar and bipolar depression are differentially affected (23). Studies have revealed that depressed patients with psychotic episodes are more impaired than non-psychotic, depressed patients (24–28). EFs in young, mild to moderately depressed patients have previously been shown to be only modestly affected, though not consistently across EF tests (7). Patients with first episode of depression have been shown to be less cognitively impaired than were patients who have had recurrent episodes (29), supporting the hypothesis that recurrence of episodes may increases the risk of cognitive impairment (30). What has not been studied, however, is the extent to which recurrent depressive episodes specifically affect EFs. Thus, one aim of the present study was to compare patients with moderate to severe, recurrent, non-psychotic, major depressive disorder with a healthy control group. We also asked if the depressed group was impaired for all sub-components of EF, and if this could be explained by medication and psychomotor retardation. The study was naturalistic in that the patients were on their regular medication when tested, and cross-sectional in that the patients were tested at only one occasion.

Material and Methods

Subjects

Forty-five patients (age range 19–51 years) with recurrent, non-psychotic, major depressive disorder according to DSM-IV (31) were included. Twenty-eight patients were inpatients, 16 were outpatients, and information about one patient was missing. The mean age at first depression episode was 25 years, and the number of episodes ranged from two to five. The patients were moderately to severely depressed, scoring minimum 18 points at both Hamilton Depression Rating Scale, 17 items (HDRS) (32) and the Montgomery–Åsberg Depression Rating Scale, 10 items (MADRS) (33). At the time of cognitive testing, three of the depressed patients were unmedicated and information regarding medication was missing for two. Thirty-six patients were on antidepressants (SSRI, mianserin, nefazodone, venlafaxine or moclobemide), and none were on tricyclic antidepressant medication. As additional medication, 19 patients were on benzodiazepines and nine on antipsychotic medication (as a hypnotic). Patients were excluded if they had alcohol or drug abuse as primary diagnosis; neurological or somatic disorders likely to affect cognitive function; recent ECT-treatment and/or lack of sufficient visual and auditory capabilities to perform the tests. Fifty healthy controls were included as a comparison group. None of the controls had a neurological, somatic or psychiatric illness known to influence cognition, or a history of alcohol or drug abuse. There were no statistically significant differences between the depressed group and the control group regarding age, level of education, gender and general abilities as measured by the Picture Completion and Similarities subtests from the revised Wechsler Adult Intelligence Scale (WAIS-R) (34). Characteristics of the patients and the controls are presented in Table 1. Written informed consent was obtained from all subjects.

Clinical evaluation and cognitive testing

The patients were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0 (SCID) (35). The severity of depression was estimated by HDRS and MADRS. The level of functioning was assessed by the Global Assessment of Functioning scale (GAF) from SCID (35). General psychopathology was assessed from the Brief Psychiatric Rating Scale (BPRS) (36). Table 1 shows mean scores for the depressed group. The inter-rater reliability was estimated according to the procedure described by Egeland et al. (37), and the average measure intra-class correlations were found to be over 0.80 for all rating scales. The neuropsychological test battery was administered within 3 days after the clinical psychiatric assessment.

The following six tests were used to assess sub-components of EF: Controlled Oral Word Association Test (COWAT) (38), Tower of London (ToL) (39, 40),

Table 1. Characteristics of the group of patients ($n = 45$) and the control group ($n = 50$).

Characteristics	Group of patients, mean (*s*)	Control group, mean (*s*)	*P*
Age (years)	35.56 (8.37)	32.92 (9.04)	0.145*
Gender (M:F)	18:27	25:25	0.328†
Education (years)	13.69 (2.77)	13.90 (2.46)	0.695*
WAIS-R			
Picture completion	9.84 (2.88)	10.50 (2.28)	0.219*
Similarities	10.82 (3.07)	11.57 (2.32)	0.183*
VSVT	15.53 (0.82)	15.87 (0.34)	–
CalCAP (s)	365.29 (85.68)	311.46 (68.04)	0.001*
HDRS	22.41 (4.42)		
MADRS	28.80 (4.39)		
GAF	46.47 (8.77)		
BPRS	43.00 (6.52)		

*Independent sample *t*-test.
†Chi-square test.
s, standard deviation; COWAT, Controlled Oral Word Association Test; WAIS-R, Wechslers Adult Intelligence Scale – Revised; VSVT, Victoria Symptom Validity Scale; CalCAP, California Computerised Assessment Package; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale.

Paced Auditory Serial Addition Test (PASAT) (41), Digits Backward (DB) from WAIS-R (34), Stroop Colour and Word Test (Stroop) (42, 43), and Wisconsin Card Sorting Test (WCST) (44). All tests were administrated and scored according to the test manuals. The six tests were selected according to the following criteria: 1) the tests had been used as EF tests in earlier studies of depressed patients, and 2) the tests were described as measures of EF components, mainly as specified by Pennington & Ozonoff (21).

The COWAT is a word generation task that assesses *verbal fluency*. An abridged version where the subject is required to generate as many words as possible within 60 seconds in response to the letter F, and then the letter A (phonemic verbal fluency) was used. The patient is then required to name as many animals and then as many clothes as possible, each within 60 seconds (categorical verbal fluency).

The ToL test requires *planning abilities*. An abridged version where the subject is given nine tasks of increasing difficulty was used. The accuracy of planning is measured by the number of trials completed within the minimum number of moves. A maximum score of 18 points is obtainable.

The PASAT and DB tests were included as tests of *working memory* in the present study. In the PASAT (45), sixty tape-recorded digits are presented twice to the subject, first with a 3-seconds and then with a 2-seconds inter-stimulus interval. The subject is instructed to add the two last presented digits and to report the sum orally. The number of correct responses at each trial is recorded. In DB, the subject has to reorganize number sequences, which consist of two to eight digits, backwards. The number of correctly reorganized sequences is recorded.

The Stroop test used in the present study was an abridged version by Commali & Kaplan consisting of three sub-tests: colour, word and colour–word. The colour–word sub-test is used as a measure of *inhibition* in the present study. We used a test that consists of three cards with either 48 coloured spots (six different colours), words of colours in black ink and incongruent words (where the colour of the word is different from the colour–word). The response time used on each card is recorded.

WCST is a complex task where several cognitive deficits may influence the *set-shifting* and problem solving ability needed to solve the task in a successful manner (46). We used a computerized version and recorded the following measures: categories completed (i.e. number of times the subject scores 10 consecutive correct items), perseverative errors (i.e. number of errors where the subject responds incorrectly but still continues to use this faulty response pattern) and failure to maintain set (i.e. number of times the subject matches five consecutive cards in a category correctly but then makes an error). The last variable was used as a measure of set-maintenance, the number of perseverative errors and the number of categories as general measures of set-shifting abilities.

In addition to the tests described above, two neuropsychological tests were also administered. These were the Victoria Symptom Validity Test (VSVT) and the California Computerised Assessment Package (CalCAP) (47). The VSVT, the 5-seconds task, was included to screen for non-optimal performance during testing and for detecting biased or random responding (48, 49). A maximum of 16 points could be obtained, and all the depressed patients achieved from 14–16 points, indicating that the depressed patients were not fatigued and did not give up. The simple reaction time subtask from the CalCAP was included as a measure of psychomotor speed in the evaluation of possible confounders. Table 1 shows that the depressed group performed significantly slower than the control group on this task.

Data analysis

The SPSS for Windows 11.0 was used for statistical analyses. Multivariate linear regression analyses were conducted to estimate a group difference between the groups of depressed patients and controls on EF. Skewed distributions on some of the EF measures were handled using power-transformation and dichotomization. Significance was obtained from regression models with transformed variables, and effect-estimates were obtained from analyses using raw-scores. The first regression model included a depression measure (a dichotomous variable) as predictor and each EF measure as dependent variable. Group differences were also illustrated using z-scores estimated for both samples together. A reliability analysis (alpha) was performed for all EF measures together, and a composite score was calculated as the mean of z-scores for these 10 EF measures. Since impairment of EF may be caused also by benzodiazepines and antipsychotic medication and/or retarded psychomotor speed in depressed patients, multivariate linear regression and stratified analyses were included to adjust for these two possible confounding factors. Psychomotor speed was operationally defined by simple reaction time from the CalCAP. The Stroop colour reading task was used to adjust for psychomotor speed in the analysis of the Stroop test, as well as a speed measure together with the CalCAP measure in a regression model. Pearson correlation was used to investigate the influence of number of depression episodes/severity of illness on cognitive performance. All statistical tests were one-tailed (because we did not expect the depressed subjects to perform better than the healthy controls) with an alpha level of 0.05.

Results

Table 2 shows that the group of patients was significantly impaired on the following eight of 10 EF measures when compared to the control group: phonemic and categorical verbal fluency from COWAT, the colour–word subtest from Stroop, the failure to maintain set and the perseverative errors variables from WCST, the PASAT measures and DB. There were no statistically significant differences between the groups on ToL and the measure categories completed from WCST. There were no more significant correlations than were expected at the 0.05 level between number of depression episodes/severity of illness and cognitive performance given the presumption that the null-hypothesis is true. Fig. 1 shows that the depressed patients performed below the control group on all EF measures. The level of impairment was variable, but mean scores on all tests within the patient group were within the range of -0.15 to -0.89 standard deviation (s) below the mean of the control group. The reliability analysis across all EF tests yielded an alpha value of 0.827. We therefore calculated the total mean EF z-score difference, which was estimated to $-2.15\ s: 10 = -0.22\ s$.

Table 2 also shows the group differences after adjusting for the use of benzodiazepines, antipsychotic medication or both. The depressed group was still significantly below the control group on the COWAT measures, the Stroop colour–word subtest, the failure to maintain set variable from WCST, the PASAT measures and the DB. There were no group differences on the ToL, or the categories completed and perseverative errors variables from the WCST. A stratified analysis was also performed and excluded patients that were on benzodiazepines and/or antipsychotic medication from the depressed group, reducing the number of patients within this group to $n = 31$. The stratified analysis gave identical results to the regression model. Table 2 shows that the use of benzodiazepines and/or antipsychotic medication reduced the results on the EF measures by approximately one-third (when comparing the crude and the adjusted for medication coefficient betas for each EF measure).

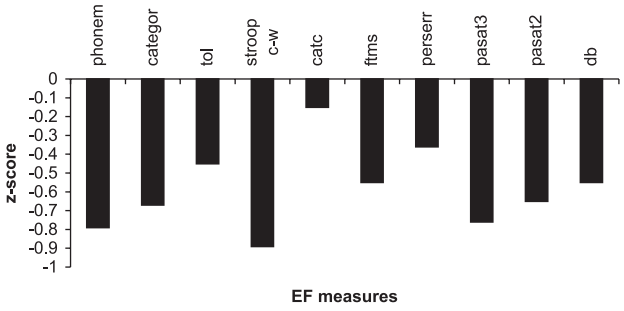

Fig. 1. Severity of impairment on the EF measures. phonem, Controlled Oral Word Association Test – phonemic verbal fluency; categor, Controlled Oral Word Association Test – categorical verbal fluency; tol, Tower of London test; Stroop c-w, The Stroop Colour Word Test – the colour–word subtest; catc, Wisconsin Card Sorting Test – Categoried completed; ftms, Wisconsin Card Sorting Test – Failure to maintain set; perserr, Wisconsin Card Sorting Test – Perseverative errors; pasat3, Paced Auditory Serial Addition Test – the 3-seconds interstimulus interval subtest; pasat 2, Paced Auditory Serial Addition Test – the 2-seconds interstimulus interval subtest; db, Digits Backward.

Table 2. Test results in the group of patients ($n = 45$) and the control group ($n = 50$).

	Control group		Group of patients		Analysis		
Neuropsychological tests	Mean	s	Mean	s	Group difference†	Adj. for medication‡	Adj. for speed‖
COWAT							
Phonemic verbal fluency	30.98	8.91	23.84	7.67	−7.14*	−5.46*	−5.39*
Categorical verbal fluency	46.63	8.94	39.89	10.09	−6.74*	−6.22*	−5.97*
ToL	16.54	1.37	15.80	1.88	−0.74	−0.33	−0.72
Stroop colour–word	43.72	9.56	54.84	13.04	11.12*	7.87*	9.07*
WCST							
Categories completed	5.29	1.62	5.04	1.62	−0.24	−0.04	−0.19
Failure to maintain set	0.73	1.27	1.62	1.81	0.89*	0.68*	0.74*
Perseverative errors	10.90	8.19	14.10	9.31	3.19*	1.86	2.61
PASAT							
3-seconds	51.96	8.63	43.21	12.80	−8.75*	−5.25*	−7.85*
2-seconds	43.44	9.53	36.00	12.26	−7.44*	−4.90*	−6.08*
DB	6.90	2.25	5.76	1.73	−1.14*	−0.80*	−0.99*

†,‡,‖P-values ≤ 0.05, one-tailed, are marked by * and based on transformed variables when needed. Coefficient B is reported.
‡Analysis adjusted for the use of benzodiazepines, antipsychotics or both.
‖Analysis adjusted for psychomotor speed as estimated by mean Simple Reaction Time, dominant hand from CalCAP.
s, standard deviation; COWAT, Controlled Oral Word Association Test; ToL, Tower of London; WCST, Wisconsin Card Sorting Test; PASAT, Paced Auditory Serial Addition Test; DB, Digits Backward.

The simple reaction time measure from CalCAP was used to adjust for the influence of psychomotor speed on the EF measures (Table 2). To avoid multi-colinearity we examined correlations between independent variables, and none correlated above 0.5. After adjusting for retarded psychomotor speed, there was still a significant group difference for all EF measures except for the ToL test, and for categories completed and perseverative errors from the WCST. Table 2 shows that retarded psychomotor speed reduced the results by approximately one-fourth (when comparing the crude and the adjusted for speed coefficient betas for each EF measure). Another regression model was included in order to examine the results on the Stroop colour–word subtest. Psychomotor speed was adjusted for by using the results from the Stroop colour subtest. This analysis confirmed that the impairment in the depressed patients could not be fully explained by psychomotor retardation. When entering the difference scores from the (colour–word)–(colour) as the dependent variable, and colour as the independent variable, this also yielded a significant group difference. The two psychomotor speed measures (CalCAP and Stroop colour) correlated with a significant Pearson's correlation coefficient of 0.255. When using both speed measures in a regression model, the results were similar to those reported under adjusted for speed in Table 2, except for perseverative errors where there was a significant difference between the groups.

Discussion

The present study was designed to examine several sub-components of EFs in depressed patients with recurrent episodes. The study showed that the performance in depressed patients was impaired compared to the control group on tests of EFs. The group differences were statistically significant for phonemic and categorical verbal fluency, Stroop colour–word, the failure to maintain set and perseverative errors from WCST, the PASAT and DB. The impairment was found to be mild, with results within -1 *s* on each test, and a composite EF score of -0.22 *s*. The use of benzodiazepines and antipsychotic medication or retarded psychomotor speed alone did not explain the cognitive impairment in depressed patients. The group was still significantly below the control group on all above-mentioned EF measures except for perseverative errors from WCST. Adjustment for additional medication and retarded speed reduced the results for each EF measure by approximately one-third to one-fourth, respectively.

According to the classifications made by Pennington & Ozonoff (21), the results indicate that the depressed patients were impaired on the EF components referred to as verbal fluency (the COWAT measures), inhibition (the colour–word subtest from Stroop), set-maintenance (the failure to maintain set variable from WCST) and working memory (the PASAT measures and DB). Set-shifting (the categories completed and perseverative errors variables from WCST) and planning abilities (ToL) appeared to be spared in this patient group. Thus, the present study showed that recurrent depressive episodes can be associated with impairments for the complex cognitive processes underlying performance on tests for EF, although it should be acknowledged that a group with single-episode depression was not included in the study. This is a limitation of the study, and should be included in future studies.

The results in the present study confirm earlier findings of deficits on verbal fluency tasks, inhibition and set-maintenance measures in depression (5–8). Our results contrast reports of a selective set-shifting deficit in depressed patients (22). Impairment in our group was restricted to the variable failure to maintain set from WCST, where impairment indicates failure to maintain set rather than impaired ability to set-shifting. The lack of impairment on the two set-shifting measures from WCST might be due to the group matching of controls and patients on intellectual abilities, a factor known to be highly correlated to results on WCST. Furthermore, there is a wide diversity of WCST results in studies of EF impairment in unipolar major depressed patients, because test performance might be influenced by which subgroup of depressed patients that is studied, the selection of EF tests, the effects of medication, hospitalisation as well as the severity of depression (9, 22). The results on ToL are also in contrast to earlier studies (9). This finding may, however, be due to a ceiling effect (lack of variance due to good performance in both groups) in the results from the version used in the present study. The present study has revealed that the sub-components most affected after recurrent episodes are verbal fluency, inhibition, set-maintenance and working memory.

All patients were on newer types of antidepressant medication, known to have less effect on cognition than the older types (9). Although we could not rule out the effect of medication in our study, the influence of benzodiazepines and/or antipsychotic medication did not change the main results. There have been studies of cognitive functions in depressed patients where the patients were medication free (7), but these studies included patients with less severe depression than in our study. For the patients with severe major depression (some with possible suicidal ideation/tendencies) included in our study, it would be unethical to discontinue medication in order to perform cognitive testing.

It has been argued that poor performance on measures of EF can be attributed to slowed psychomotor speed (50). Such a slowness is widely documented in patients with depression (4), and our sample of depressed patients showed retarded psychomotor speed

when compared to controls. The main result of mild impairment across a wide range of EF tests was replicated even when psychomotor speed was statistically adjusted for. When adjusting for an internal measure of psychomotor speed (colour) on the Stroop colour–word subtest, we found that the depression group performed significantly more slowly than controls on the colour and the colour–word subtests, but not the word subtest. After subtracting the colour from the colour–word results, there was still a significant difference between the groups for the colour–word subtest. This might indicate that when cognitive effort is called upon in order to inhibit more automatic responses on the colour–word subtask, the patients show deficits. From the results on the VSVT, it seems that the depressed patients are as motivated as the controls to perform the tests.

The clinical significance of the findings can be inferred from the *z*-scores calculated for the patient group. We found the impairment to be mild, because all results in the depressed group were within -1 *s* from the mean in the control group. On the other hand, subtle deficits on a wide range of EF measures may have clinical, social and occupational consequences for patients with recurrent unipolar depression.

It is still not evident whether cognitive impairment is a state or a trait problem, or if it represents both state and trait factors in depression (51). This should be explored in future longitudinal studies.

In conclusion, the present study showed that a group of patients with unipolar major depression with recurrent episodes and without psychotic features performed more poorly on measures of verbal fluency, inhibition, set-maintenance and working memory compared to a control group, after adjusting for additional medication and retarded psychomotor speed. Although the impairment was mild, the consistent lower performance across EFs may have clinical implications in regards to activities of daily living. In future studies, one should explore the pattern of impairment in individual patients, the relationship between function in everyday life and performance on cognitive tests, as well as the possibility of a persisting impairment in the non-symptomatic phase.

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