

# Paper II



ORIGINAL INVESTIGATION

## Frequency and characteristics of recurrent major depressed patients with unimpaired executive functions

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### Abstract

Major depression is associated with impairment of cognitive functions, and especially higher-order cognitive processes referred to as executive functions (EF). Whether this is a general finding is unclear. Patients without EF impairment may have different treatment needs than patients with EF impairment, and will probably have a better everyday functioning. Thus, it is important to identify the prevalence and characteristics of depressed patients without EF impairment. Forty-three patients with recurrent major depressive disorder (19–51 years) and 50 healthy controls were included in the study. The subjects were assessed with neuropsychological tests selected to measure central areas of EF, and screened on clinical and demographic variables. Within the depressed group, a total of 56% were defined as EF unimpaired. These patients were characterised by higher intellectual abilities and fewer depression episodes than the subgroup of patients with EF impairment. The subgroups were similar in age at debut of illness, severity of depression, general psychopathology and global level of functioning. In conclusion, about half of patients with recurrent major depression have normal EF. Since cognitive impairment and depressive symptomatology seem to be distinct dimensions, a neuropsychological investigation could help to ensure optimal treatment in patients with recurrent major depression.

**Key words:** Major depression, non-psychotic, recurrent, neuropsychological tests, executive functions

### Introduction

Major depression is a serious condition with a lifetime prevalence of 17% (Angst 1999). The majority of patients experience recurrence of episodes after recovery (Mueller 1999), and the risk of psychosocial impairment is high (Angst 1999).

It is commonly accepted that higher-order cognitive functions, the so-called executive functions (EF), are impaired in major depression on a group basis (Degl'Innocenti et al. 1998; Elliott 1998; Fossati et al. 1999; Merriam et al. 1999; Grant et al. 2001; Stordal et al. 2004). EF can be defined as a set of processes involved in complex intentional behaviour that 'control, integrate, organise and maintain other cognitive processes' (Pohjasvaara et

al. 2002). The concept can further be divided into several subcomponents (Lezak 1995), i.e. Pennington and Ozonoff's (1996) subdivision into verbal fluency, planning, working memory, inhibition, set-shifting and set-maintenance. These subcomponents can be operationalized by specific neuropsychological tests. The EF impairment as well as the depressive symptoms have been associated with dysfunction of frontal-subcortical systems (Mega and Cummings 1994; Goodwin 1997; Elliott 1998; Royall 1999; Mazziotta et al. 2000).

EF impairment has been suggested to be an early sign of cognitive impairment in patients with major depression (Austin 2001). The EF domain also seems impaired in drug-free patients (Porter et al. 2003). It has also been shown that EF are affected in

depressed patients who are in the remission or recovery phase of the disorder (Elliott 1998; Reischies and Neu 2000; Grant et al. 2001). The level of EF dysfunction in depressed patients is, however, disputed. Some studies have indicated that major depressed patients perform at the same level as controls on cognitive tests (Grant et al. 2001), whereas other studies have compared their performance to that of patients with traumatic brain-damage (Veiel 1997). In a recent study, patients with recurrent major depression performed significantly below that of healthy controls on tests of EF, but the severity of the impairment on a group basis was shown to be within the range of  $-0.15$  to  $-0.89$  standard deviations (S.D.) below the mean of the control group (Stordal et al. 2004).

There is, however, a general agreement that EF are essential for complex activities of daily living (Grigsby et al. 1998). A recent report from a study of patients with unipolar depression indicated that EF impairment predicted non-response to fluoxetine, and it was suggested that EF assessment in depressed patients could 'play a particular role in the pretreatment identification of subjects likely to respond to specific medications' (Dunkin et al. 2000). It is also possible that unimpaired EF can be a positive prognostic factor in patients with major depression, as suggested for patients with schizophrenia (Palmer et al. 1998). Thus, one should expect that depressed patients with normal EF will benefit more from pharmacotherapy and will have better everyday functioning than their EF impaired counterparts. From a clinical point of view, it is therefore of interest to know more about the frequency of depressed patients with normal EF and their clinical characteristics. In general, there is a lack of studies that identify depressed patients who are neuropsychologically normal, and in particular studies identifying EF unimpaired depressed patients.

In order to identify unimpaired patients, a careful selection of EF measures and a cut-off value to define EF unimpairment is needed. There is no generally accepted cut-off point for defining unimpairment or impairment in depressed patients. Heinrichs (2001) refers to  $-2.0$  S.D. as the most often used cut-off value for neuropsychological impairment, whereas  $-1.5$  S.D. was used as cut-off point defining EF impairment in a group of post-stroke depressed patients (Pohjasvaara et al. 2002). Palmer et al. (1997) used a combination of both neuropsychological test summary scores and neuropsychologist expert ratings in their evaluation of neuropsychological impairment in schizophrenic patients, while Newman et al. (2001) underscored the need to be impaired on more than one functional

measure to be defined as impaired. Thus, the question of impairment seems to be relative.

In the present study, a group of patients with recurrent major depression and a healthy control group were included and assessed on a set of tests measuring different subcomponents of EF. Impairment was defined from the distribution in the control group. The aim was to explore group differences between depressed patients and controls in EF. Then we estimated the prevalence of depressed patients without EF impairment and their clinical characteristics. We also wanted to explore whether EF was equally affected by age, level of education, sex and intellectual abilities in depressed and non-depressed subjects.

## Material and methods

### *Subjects and clinical assessment*

Forty-three depressed patients (age range 19–51 years) were included in the present study. The subjects have previously been described elsewhere (Egeland et al. 2003a,b; Stordal et al. 2004), but in this study two of the original patients were excluded because of missing data on one of the neuropsychological EF tests. The patients were examined at five different psychiatric hospitals in Bergen and Oslo, Norway. They were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I version 2.0) (First et al. 1995), and all subjects met DSM-IV diagnostic criteria for major depressive disorder, recurrent type without psychotic features (American Psychiatric Association 1994). The age at onset of depression ranged from age 7 to age 44, and the number of depression episodes from two to five ( $n=26$  due to missing data). The patients were moderately to severely depressed, scoring a minimum of 18 points at the Hamilton Depression Rating Scale, 17 items (HDRS) (Hamilton 1960) and 21 points at the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979). The daily psychological, social and occupational functioning of the depressed patients was assessed with the Global Assessment of Functioning scale (GAF) from SCID (First et al. 1995). An indication of the general psychopathology of the patients was given by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). At the time of cognitive testing, three of the depressed patients were unmedicated and information regarding medication was missing for two. Thirty-four patients were on antidepressants (SSRI, mianserin, nefazodone, venlafaxine or moclobemide), and none were on tricyclic antidepressant medication. As additional medication, 17

patients were on benzodiazepines and eight on antipsychotic medication (as a hypnotic). A healthy control group ( $n=50$ ) was recruited from the local communities. The two groups were matched on age, gender, level of education and intellectual abilities as assessed by the Similarities test from the Revised Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler 1981). There were significant group differences for the Picture Completion test (Wechsler 1981) (Table I). The study was approved by the Regional Committee for Medical Ethics. All participants provided written informed consent to participate in the study.

*Neuropsychological assessment and operationalization of EF*

The neuropsychological assessment was performed within 3 days after the clinical psychiatric assessment. Each participant completed a set of neuropsychological tests, selected to assess central areas of executive functioning and intellectual abilities. A prior report showed that only some of the included EF tests separated depressed patients from non-depressed controls after adjusting for additional medication (benzodiazepines and antipsychotics) and psychomotor retardation (Stordal et al. 2004). These tests were the Paced Auditory Serial Addition Test (PASAT), the Digit Backward subtest (DB) from WAIS-R, the Controlled Oral Word Association Test (COWAT), the Failure to Maintain Set variable from Wisconsin Card Sorting Test (WCST) and the Colour-Word subtask from the Stoop Colour Word Test (Stoop). These five tests were used as measures of four different subcomponents or areas of EF. The PASAT measure (the sum of the 3- and 2-second interstimulus interval subtests) and the DB measure were used to assess working memory. The sum of words from the four COWAT subtests was used as a measure of verbal fluency. The WCST score was used as a set-maintenance measure and the Stroop variable as a measure of inhibition (Table I).

*EF summary score*

For the depressed group, the results from the four measures were normalised. Standardised scores were then calculated for the set-maintenance, inhibition, verbal fluency and working memory measure results. A Cronbach's coefficient alpha of 0.701 was found for the  $z$ -scores calculated from the four EF measures. The results from these scores were then summarised to obtain a continuous EF summary score.

Table I. EF and intellectual abilities tests and test results for the depressed group ( $n=43$ ) and the control group ( $n=50$ ).

	Assessment	Score	Control group M (SD), range	Depressed group M (SD), range	Choen's $d$	$T$ -test sign.
Executive function tests						
PASAT (Gronwall 1977)	Working memory	Number of correct summations from the sum of 3- and 2-sec interstimulus intervals	95.40 (16.58), 45–120	79.21 (24.28), 24–118	0.78	0.000
DB (Wechsler 1981)	Working memory	Number of correct repeated sequences	6.90 (2.25), 3–13	5.81 (1.67), 3–11	0.55	0.001
COWAT (Benton and Hamsher 1989)	Verbal fluency	Total score of four components: letter F, letter A, animals and clothes	77.27 (15.42), 47–111	64.26 (15.68), 28–93	0.84	0.000
WCST (Heaton et al. 1993)	Set-maintenance	Number of failures to maintain set	0.73 (1.27), 0–6	1.49 (1.65), 0–6	0.52	0.007
Stroop (Mitrushina et al. 1999; Stroop 1935)	Inhibition	Response time (sec) reading aloud incongruent colours (colour-word)	43.72 (9.56), 24–68	54.37 (12.97), 33–85	0.93	0.000
Intellectual abilities tests						
Similarities (Wechsler 1981)	Verbal abilities, abstraction	Number of correct answers	21.14 (4.31), 2–28	19.91 (5.52), 4–27	0.25	0.232
Picture completion (Wechsler 1981)	Visual analyse, concentration	Number of correct answers	15.92 (2.22), 10–19	14.69 (3.09), 6–19	0.46	0.029

*Definition of EF unimpairment*

Because low performance in one cognitive domain is frequent among normal subjects (i.e. Heaton et al. 1991), impaired performance in several EF measures should be required to define EF impairment. The exact number of areas was defined from the distribution in the control group (Table II) which show that the majority of controls was impaired in zero or one areas. EF unimpairment was defined from the distribution of EF scores in the control group (Table II). We considered 84% of the controls to be unimpaired as a reasonable number. Thus, we defined the cut-off point for EF impairment as performance equal to or below  $-1.0$  S.D. in the control group on more than one area of EF (see Table II) and accordingly unimpairment as performance above  $-1.0$  S.D. (a good definition of impairment should probably identify a smaller proportion of the population). To be defined as impaired on working memory, both the PASAT and the DB scores had to be impaired.

*Data analysis*

The SPSS for Windows 11.0 was used for statistical analyses. Skewed distributions were handled using power-transformation (the Stroop measure) or dichotomization (the WCST variable) and standardised scores ( $z$ -scores) were calculated using standardised procedures in SPSS. Choen's  $d$  was used as a measure of effect-size (Rosnow et al. 2000). To explore associations between demographic/clinical characteristics and EF impairment, linear and categorical analyses were performed using Pearson correlation and Student  $t$ -test/Pearson Chi-square test, respectively. A multivariate regression model was used to explore the interaction between demographics/intellectual abilities and diagnosis (dichotomous variable indicating depression or non-depression) in the prediction of EF impairment. In this model, the EF summary score was treated as dependent variable (i.e. level of EF impairment = diagnosis + age + age  $\times$  diagnosis). Demographic and intellectual abilities variables were dichotomised according to the median value for all subjects and used as independent variables. All statistical tests were two-tailed with an  $\alpha$  level of 0.05.

**Results**

There were large and statistically significant group differences between depressed patients and controls on all selected EF measures (Table I).

Clinical and demographic characteristics of the seven best and the seven worst performing individuals in EF are shown in Table III. Among the seven patients performing below  $-1.0$  S.D. in EF, all were on antidepressants, none were on antipsychotic medication and only one was on sedatives (benzodiazepines). Of the seven patients performing above  $1.0$  S.D., one was on antipsychotic medication, four were on sedatives and two were unmedicated with regard to antidepressant medication.

According to the definition of EF unimpairment, 56% of the depressed patients were defined as EF unimpaired (Table II). EF unimpairment was present in both depressed patients and controls, but there was significantly more EF unimpairment in the control group than in the depressed group. Sixteen percent of the controls were EF impaired. Thus, although statistically significant, there were EF impaired subjects in the control group and patients without EF impairment in the depressed group. An odds ratio of 4.2 (95% C.I., from 1.6–10.9) indicated that the odds of EF impairment was approximately four times higher in the depressed group than in the control group. An explained variance of 10% was found. In other words, 90% of the variance in EF could be explained by other factors. Thirty-five percent of the depressed patients had zero impaired EF areas as compared to 54% of the controls. The four different EF areas did not discriminate equally between depressed patients and controls (Table IV). The greatest difference was seen for verbal fluency followed by inhibition, set-maintenance and working memory.

In the linear analyses, no statistically significant correlations were found between the EF summary score and the following clinical variables: in/out patient, age at onset, number of episodes, severity of depression, level of general psychopathology and global level of functioning (Table V). The mean age in the control group was 32.9 years compared to 35.2 years in the depressed group. The mean level of education in years for the control group was 13.9

Table II. Percentage of depressed group ( $n=43$ ) and control group ( $n=50$ ) that perform equal to or below cut-off point on from zero to four of the EF areas, and total percentage of each group that are without and with EF impairment.

	0 areas (%)	1 area (%)	2 areas (%)	3 areas (%)	4 areas (%)	Without imp $n$ (%)	With imp $n$ (%)	Total $n$ (%)
Depressed group	34.9	20.9	23.2	14.0	7.0	24 (55.8)	19 (44.2)	43 (100)
Control group	54.2	33.3	8.3	2.1	2.1	42 (84)	8 (16)	50 (100)

Chi-square test,  $P < 0.001$

Table III. Clinical and demographic characteristics of the seven worst ( $< -1.0$  S.D.) and seven best ( $> 1.0$  S.D.) performing individuals in EF.

EF summary $z$ -score	Age group	Sex	Education	In/Out patient	GAF	BPRS-E total	HDRS total	MADRS total
-1.75	30	M	15	In	40	41	26	31
-1.74	30	F	17	Out	65	38	19	28
-1.55	20	M	18	Out	40	42	27	31
-1.46	30	F	18	Out	50	47	22	36
-1.26	30	M	13	In	35	43	21	36
-1.20	20	F	10	In	50	52	26	30
-1.08	50	F	18	Out	50	47	26	31
1.07	40	F	15	In	45	50	27	35
1.18	40	F	12	Out	45	42	27	25
1.21	30	M	17	Out	55	46	20	24
1.26	30	F	12	Out	45	36	18	26
1.45	30	M	13	In	55	42	21	23
2.00	20	F	11	In	45	51	23	31
2.15	40	M	9	In	45	43	23	31

compared to 13.8 for the depressed group. As for the measures of intellectual abilities, controls had a mean scaled score of 10.5 on the Picture Completion test and 11.6 on the Similarities test from WAIS-R, whereas depressed subjects had 9.8 and 10.9, respectively. There were statistically significant correlations between level of EF and age (Pearson correlation = 0.349,  $P=0.022$ ), education (Pearson correlation = -0.425,  $P=0.005$ ), and intellectual abilities as measures with the Picture completion (Pearson correlation = -0.557,  $P<0.001$ ) and the Similarities (Pearson correlation = -0.690,  $P<0.001$ ) subtasks.

In the categorical approach, a statistically significant group difference between the EF unimpaired and impaired subgroups for the number of episodes variable was found, with a lower number of depression episodes in the non-impaired group. There were no statistically significant differences between the groups regarding the following clinical variables: in/out patient, age at debut, severity of depression, level of general psychopathology and global level of functioning. The results from the categorical approach were therefore similar to the result from the linear approach. The mean age in the control group without EF impairment was 33.4 years compared to 33 years in the depressed group. The mean age in

the control group with EF impairment was 30.3 years compared to 37.9 years in the depressed group. As for the measures of intellectual abilities, controls without EF impairment had a mean scaled score of 10.6 on the Picture Completion test and 11.4 on the Similarities test from WAIS-R, whereas depressed subjects had scores of 10.3 and 11.9, respectively. In the EF impaired subgroups, controls showed a mean scaled score of 9.9 on the Picture Completion test and 12.6 on the Similarities test compared to 9.2 and 9.7 for the depressed subgroup. A statistically significant group difference was found for intellectual abilities as measured with the Similarities test ( $t=2.535$ ,  $P<0.015$ ), but not for age ( $t=-1.948$ ,  $P<0.058$ ) and education ( $t=1.719$ ,  $P<0.093$ ), although these variables almost reached significant levels. The depressed patients without EF impairment were thus characterised by fewer depression episodes and higher intellectual abilities than patients with EF impairment, but the groups were similar on measures of symptomatology, general psychopathology and global functioning.

For the interaction between age and diagnosis in prediction of level of EF performance (the EF summary score) a  $\beta$  value of 0.286 was found ( $P<0.093$ ) in the linear regression model. In other words, subjects both being depressed and older than

Table IV. Distribution of depressed group ( $n=43$ ) and control group ( $n=50$ ) in the four EF areas: inhibition, set-maintenance, verbal fluency and working memory.

	Depressed patients		Controls	
	Equal to/below cut-off point (%)	Above cut-off point (%)	Equal to/below cut-off point (%)	Above cut-off point (%)
Inhibition	39.5	60.5	16	84
Set-maintenance	41.9	58.1	22.4	77.6
Verbal fluency	44.2	55.8	16.3	83.7
Working memory	11.6	88.8	8	92

Table V. Clinical variables and EF impairment in the depressed group ( $n = 43$ ), and subgroups without ( $n = 24$ ) and with ( $n = 19$ ) EF impairment.

	Depressed M (SD)	Pearson Correlation <sup>a</sup>	Without imp M (SD)	With imp M (SD)	Sign. 2-tailed
In:Out patients (%)	61.9:38.1	-0.090	61:39	63:37	0.879 <sup>c</sup>
Age at debut (years)	23.6 (9.5)	0.225	21.5 (7.9)	26.2 (11.0)	0.116 <sup>d</sup>
Number of episodes <sup>b</sup>	3.8 (2.9)	0.184	2.8 (0.9)	3.8 (1.2)	0.017 <sup>d</sup>
HDRS total	22.5 (4.5)	-0.095	22.2 (3.7)	22.8 (5.4)	0.687 <sup>d</sup>
MADRS total	28.8 (4.5)	-0.083	28.8 (4.9)	28.8 (4.1)	0.975 <sup>d</sup>
BPRS-E total	43.2 (6.6)	0.146	43.0 (8.1)	43.3 (4.2)	0.894 <sup>d</sup>
GAF	46.7 (8.8)	0.008	46.7 (10.6)	46.7 (6.0)	0.995 <sup>d</sup>

<sup>a</sup> Significant correlations are marked with ‘\*’.

<sup>b</sup>  $n = 26$ : non-impaired subgroup ( $n = 14$ ), impaired subgroup ( $n = 12$ )

<sup>c</sup> Chi-square test.

<sup>d</sup> Student  $t$ -test.

the median value were more likely to be EF impaired. There were no significant interactions between diagnosis and education, sex, or intellectual abilities as measured with either the Picture Completion test or the Similarities test from WAIS-R.

### Discussion

In the present study a significant and large group difference between depressed patients and controls was found for all selected EF measures. This finding is in line with previous studies (i.e. Degl’Innocenti et al. 1999; Austin et al. 2001; Stordal et al. 2004). However, the study points to the fact that still a significant proportion of patients with recurrent major depression show unimpaired EF when moderately to severely depressed. Furthermore, patients without EF impairment according to our definition were similar to patients with EF impairment regarding clinical variables such as severity of depression, general psychopathology and global functioning, but they were characterised by fewer depression episodes and higher intellectual abilities than patients with impairment.

The definition of unimpairment chosen in this paper can be disputed. The number of impaired patients in the present study is higher than that reported in a study by Reischies and Neu (2000). They found that about a third of depressed patients were impaired on measures of fluency and memory, but they used the fifth percentile as cut-off point. EF impairment in groups of patients with major depression is frequently reported in the literature (i.e. Degl’Innocenti et al. 1998; Fossati et al. 1999; Stordal et al. 2004), although some studies have not found EF impairment or only modest evidence of such (Purcell et al. 1997; Grant et al. 2001). The association between major depression and EF impairment, which seems to be a strong association due to the tendency of mostly positive findings in the

literature, can therefore put an extra ‘illness burden’ to an already severely ill group of patients. To the best of our knowledge, the present study is the first to focus on the recurrent major depressed patients with unimpaired EF, although similar studies have been performed on other depressed patient samples, schizophrenic patients as well as patient groups with neurological diseases (Palmer et al. 1997; Reischies and Neu 2000; Pohjasvaara et al. 2002). It has shown that, although major depressed patients show EF impairment on a group basis (Stordal et al. 2004), this study has shown that not all patients within the group are EF impaired. The present study shows that the association between major depression and EF impairment is rather weak. Not only are many patients unimpaired on EF tests, but most of the variance in EF could be explained by other factors than the depression itself. These findings underscore that there is large heterogeneity within the groups of recurrent major depressed patients with respect to EF impairment.

Because one main hypothesis is that each repeated depression episode ‘leaves a mark’ in the brain (Sheline 2000), only patients with recurrent major depression were included in the study. Although the depressed patients with EF impairment in the present study had more depression episodes than the patients without such an impairment, other studies have not found such an association (Reischies and Neu 2000). The present study has also demonstrated that the EF impairment found in major depressed patients does not seem to be associated with clinical variables as severity of depression, general psychopathology and functioning, although this could be expected from a clinical point of view. Also this finding is in agreement with some of the prior studies (i.e. Degl’Innocenti et al. 1998), but not others (i.e. Grant et al. 2001). In fact, it is striking how inconsistent the results in the literature are when correlating clinical variables to

cognitive performance. This inconsistency may in part be explained by a large percentage of patients being neuropsychologically normal. Furthermore, a longitudinal study by Rieschies and Neu (2000) showed that patients with cognitive impairment were still impaired when recovered from their depression. The cognitive impairment and the depressive symptomatology therefore seem to be distinct dimensions.

There was a tendency towards age playing a larger role for EF performance in depressed patients than in control subjects. It is an established fact that with increasing age there is a decline in cognitive functions. However, in schizophrenic patients, a larger age-related decline was found in EF (abstraction) compared to other cognitive functions (Fucetola et al. 2000). Thus, it is possible that recurrent depression per se may accelerate the natural ageing processes of the brain. But this does not explain why only a small subgroup of the recurrent depressed patients was EF impaired. Another explanation is that the EF impaired subgroup can be more at risk for the development of dementia, although O'Brien et al. (2001) found no relation between cognitive impairment in depression and dementia in a neuropathological study. The relation between depression and age in prediction of EF impairment should be explored in further studies.

The strengths of the present study include use of a well-defined depression sample, well-matched controls and several neuropsychological tests assessing different aspects of EF. However, there are several limitations to the study. Firstly, the patients included in the present study were on antidepressant drugs when neuropsychologically tested. There is a possibility that in an unmedicated sample, the percentage of EF impaired depressed patients would be higher. Secondly, the patients were also rather homogeneous with respect to symptoms of depression due to the specified inclusion criteria. The association between level of performance on tests of executive function and clinical symptomatology should thus be examined in a more heterogeneous sample of depressed patients. Third, the selection of EF variables is critical. The failure to maintain a set variable from the WCST is a somewhat problematic and complex measure and may not be the best variable to operationalise EF. Still, this measure was the only WCST variable that separated depressed patients from healthy controls in a former study (Stordal et al. 2004), and it has been used in earlier studies of depressed patients as an EF variable (Degl'Innocenti et al. 1998; Grant et al. 2001). And, finally, since there is no generally accepted standard for defining EF impairment in depressed patients, our choice of cut-off point may be criticised.

In conclusion, our results with regard to group differences between depressed and non-depressed subjects in EF are in accordance with previous studies. Despite this large group difference, we found that 56% of depressed patients still are unimpaired in EF when unimpairment is defined from the distribution in the control group. A recent report showed that major depressed patients with EF impairment were non-responders to fluoxetine (Dunkin et al. 1999). It is therefore possible that patients with EF impairment to a lesser extent benefit from pharmacotherapy, and probably also from psychotherapy compared to patients with normal EF. A recent report showed problem-solving therapy to be more effective than supportive therapy in reducing depressive symptoms and disability in elderly patients with major depression and EF dysfunction (Alexopoulos et al. 2003). Since cognitive impairment and clinical symptomatology seem to be distinct dimensions in recurrent major depression, a neuropsychological investigation may be included to identify patients with special treatment needs in order to ensure optimal treatment. In future studies one should thus be aware of the heterogeneity of recurrent depressed patients with respect to cognitive impairment, and explore the association between major depression and cognitive impairment in longitudinal studies.

#### Acknowledgements/Statement of interest

The present research was financially supported by grants to Bjørn Rund from the Research Council of Norway (NFR), # 122974/320 and the National Council for Mental Health/Norwegian Foundation for Health and Rehabilitation (#1997/007).

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