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ORIGINAL ARTICLE

Cognitive impairment in unipolar depression is persistent and non-specific: further evidence for the final common pathway disorder hypothesis

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Background. Cognitive performance is often impaired in depression, and these impairments can persist even after remission from psychopathological symptoms. However, it is still unclear whether cognitive dysfunction is associated with psychopathological symptoms or represents a genuine disorder. This study examined cognitive performance in acute depression, after remission, and 6 months after remission in order to determine the nature and specificity of cognitive dysfunction as well as its relevance for the further course of depression.

Method. Assessments of cognitive function and psychopathology were carried out on admission and prior to discharge in 53 in-patients with unipolar depression. Twenty patients were retested 6 months after discharge. To correct for practice effects, 13 healthy subjects were included and assessed twice with the same cognitive tests.

Results. In acute depression, we found impairments of information processing/attention, memory, and executive functions. Cognitive impairments remained in a high proportion of patients, even after remission of psychopathological symptoms. After correcting for practice effects, a significant improvement was observed only for some tests of executive functioning. Severity of depression was only weakly correlated with one single cognitive measure, indicating that psychopathological and neuropsychological symptoms are dissociable. Furthermore, we found no evidence for specific cognitive dysfunction.

Conclusions. Our results support the hypothesis that cognitive impairments in depression are neither selective nor specific; they have trait-like features and are, therefore, not merely an epiphenomenon of depression. Whether or not cognitive dysfunction is a prognostic marker for the course of depression remains still an open issue.

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Introduction

With a lifetime prevalence of 11.5% in Germany and up to 16.9% in the USA, major depression is one of the most frequent disorders (Andrade *et al*. 2003). In addition to affective symptoms such as altered mood and behaviour, cognitive function is also often impaired. Disturbances in concentration represent a standard operational criterion for the diagnosis of major depression according to DSM-IV criteria (APA, 1994). Impairments of cognitive function have been found across a range of cognitive domains, including memory (Bearden *et al*. 2006), attention (Zihl *et al*. 1998) and executive functions (Stordal *et al*. 2004).

Ascertaining whether cognitive impairments diminish or persist despite improvement of psychopathological symptoms is a fundamental issue for optimizing treatment in depressed patients. There is substantial evidence for the persistence of cognitive deficits even after remission of depressive symptoms (Marcos *et al*. 1994; Weiland-Fiedler *et al*. 2004; Neu *et al*. 2005; Reppermund *et al*. 2007). Neu *et al*. (2005) reported persistent cognitive deficits in verbal memory and verbal fluency in middle-aged depressed patients after treatment, even after being in a euthymic state for at least 6 months. In contrast, Weiland-Fiedler *et al*. (2004) found no evidence of impaired visual memory and learning in drug-free, remitted patients in comparison with healthy controls. However, they suggest deficits in sustained attention as a vulnerability marker for major depression. Although there is no cognitive function that is solely impaired in remitted patients, all of these studies indicate that cognitive dysfunction is trait-dependent and not merely an epiphenomenon of psychopathological symptoms (Murphy *et al*. 1998; Austin *et al*. 2001).

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Neuroimaging studies suggest that depression is associated with abnormal changes in different brain structures including the prefrontal cortex, anterior cingulate, striatum and medial temporal lobe (Bench *et al*. 1993; Dolan *et al*. 1994; Ebmeier *et al*. 2006). It is possible that cerebral dysfunction does not necessarily recover completely and may therefore contribute to persistent neuropsychological impairments (Holthoff *et al*. 2004; Strakowski *et al*. 2005).

Moreover, previous studies investigating cognitive functioning in depression suggest that cognitive impairment may predict the further course of illness. Executive dysfunctions in particular were claimed to be predictive of poor treatment response, non-remission and elevated risk to relapse (Alexopoulos *et al*. 2000; Majer *et al*. 2004). Alexopoulos *et al*. (2000) found that deficits in executive function (abnormal initiation, perseveration) predict relapses and recurrences of depressive episodes 2 years after discharge. However, cognitive assessment was solely based on a screening instrument and their study included elderly patients only. Majer *et al*. (2004) observed generalized cognitive impairments across all cognitive domains. However, they regarded the impairment of divided attention as a more specific deficit within the domain of attention because neither reduced sustained attention nor impaired selective attention accounted for this impairment. As particularly non-responders showed impaired divided attention on admission, the authors speculated whether this deficit might represent a marker for predicting the further course of depression. However, they found only a trend for the association between impaired divided attention and an elevated risk to relapse. Weiland-Fiedler *et al*. (2004) found sustained attention to be a possible predictor for the course of depression.

Although it is now widely accepted that cognitive dysfunction is a genuine feature of depression, the nature and specificity of cognitive deficits in depression remain unclear. Whereas Fossati *et al*. (1999) found predominantly executive dysfunctions, others reported primarily memory disturbances (Lemelin *et al*. 1996; Basso & Bornstein, 1999; Sweeney *et al*. 2000) or rather generalized impairments in most cognitive domains (Majer *et al*. 2004). Thus, a consistent and clear-cut profile of cognitive impairments has not been established hitherto. Some authors (Mialet *et al*. 1996; Zihl *et al*. 1998) have therefore interpreted the rather unspecific cognitive deficit pattern as a final common pathway disorder, emphasizing the particular role of deficits in intensity and selectivity of attention and its executive components. The idea of a final common pathway disorder is based on the assumption that mainly supramodal functional networks are affected, which represent the highest and final level of integration of regional cognitive networks subserving, e.g. information processing, attention and memory. This idea is further supported by brain imaging studies in normal (Kane & Engle, 2002) and in depressed subjects (Austin *et al*. 2001; Rogers *et al*. 2004), which have shown that the prefrontal cortex plays the dominant role as final common pathway.

To date, very few longitudinal studies exist that have assessed associations between cognitive function and the course of depression. Due to small sample sizes, restriction to elderly patients and the failure to control for practice effects, findings should be regarded as preliminary. Furthermore, the majority of investigations are confined to exploring single domains rather than defining a comprehensive cognitive profile of depression.

The present study examined cognitive performance in young to middle-aged depressed in-patients in acute status, after remission of psychopathological symptoms following treatment, and 6 months after remission in order to determine the nature and specificity of cognitive dysfunctions as well as its relevance for the further course of depression. We investigated whether there is a significant relationship between cognitive dysfunction and psychopathology or whether cognitive dysfunction represents an independent syndrome complex. In addition, we examined whether remission of depression is related to remission of cognitive dysfunction. Finally, we investigated the role of cognitive disorders as a potential neuropsychological marker for the course of depression. To address these research questions, we applied a comprehensive neuropsychological assessment comprising the domains of information processing/attention, memory, and executive functions.

Methods

Subjects

Fifty-three depressed in-patients (28 female, 25 male), admitted to the Max Planck Institute of Psychiatry in Munich, were included. Inclusion criterion was unipolar depression with either a first episode of major depression ($n=16$) or recurrent depression ($n=37$). The mean age of subjects was 43.5 (range 22–58) years. Depression in patients was diagnosed by trained psychiatrists according to DSM-IV criteria. Depression ranged from moderate to severe, scoring a minimum of 14 points (mean 25.1, S.D. = 5.1) on the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960).

Subjects with depression secondary to a neurological or physical illness, electroconvulsive therapy within the past 3 months, current substance abuse,

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Table 1. *Demographic and clinical characteristics of participants*

	Patients ($n=53$)	Controls ($n=13$)	Statistical test	p
Age, years	43.5 (8.0)	46.4 (9.5)	$t(64)=-1.14$	N.S.
Age range, years	22–58	23–58		
Gender, *n*			$\chi^2=0.004$	N.S.
Males	25	6		
Females	28	7		
Education, years	10.5 (1.4)	10.6 (1.2)	$t(64)=-0.17$	N.S.
No. of previous episodes	2.7 (3.4)			
Age at onset, years	32.5 (10.3)			

N.S., Non-significant.

Values are given as mean (standard deviation), range or as *n*.

dementia, insufficient visual or auditory functions, or German language capabilities were excluded from the study. Patients were treated according to the doctor's choice with different kinds of antidepressants, with dosage adjusted according to clinical improvement and plasma levels. At initial assessment all but three subjects received antidepressive medication.

Additionally, 13 control subjects (seven female, six male) from a Munich-based community sample with no lifetime history of psychiatric Axis I disorders were recruited. The groups were matched for age, gender and education (see Table 1); absence of Axis I disorders was ascertained by computer-assisted interviews with a modified version of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI; Wittchen & Pfister, 1997).

The study was approved by the ethics committee of the Ludwig-Maximilians-University (Munich, Germany), and all subjects gave written informed consent prior to study inclusion.

Study design

Cognitive and psychopathological assessments were performed twice, i.e. on admission (within 3–10 days following admission to the hospital) and prior to discharge (last week before discharge). Cognitive tests were administered in the forenoon. To avoid fatigue effects, neuropsychological assessments were performed on 2 consecutive days. Course and severity of depressive symptoms and response to the pharmacological treatment were assessed using the HAMD by trained psychiatrists and psychologists. The mean interval between the first and second cognitive assessment was 9 (S.D. = 4.8) weeks.

An additional cognitive and psychopathological assessment was carried out in a subsample of 20 patients (10 female, 10 male; mean age 41.7, S.D. = 7.1 years), who were remitted at the time of discharge; these patients were re-examined about 6 months (mean = 5.6 months) thereafter.

To estimate the effects of test repetition, control subjects were assessed twice with the same cognitive tests at intervals of 4.4 weeks (S.D. = 0.6 weeks). This time interval corresponds to the shortest hospitalization period of the patient group.

Neuropsychological assessment

Cognitive functions were assessed in a fixed sequence with the following standardized tests.

Information processing/attention

The subtest 'Alertness' of the 'Testbatterie zur Aufmerksamkeitsprüfung' (TAP; Zimmermann & Fimm, 1993) measures alertness in terms of responses to a visual stimulus with and without a warning tone. Performance is assessed by measuring reaction time (ms).

The 'Zahlenverbindungstest' (ZVT; Oswald & Roth, 1987) is a trail-making test and was used to assess speed of information processing. It consists of four matrices, each comprising numbers from 1 to 90 arranged pseudorandomly on a sheet of paper. The subjects were instructed to join the numbers in ascending order as quickly as possible. In the present study, two matrices were administered (ZVT-A, ZVT-B), and the average time was used as a measure of cognitive speed performance.

The 'Aufmerksamkeits-Belastungstest d2' (Brickenkamp, 2002) is a paper-and-pencil speed cancellation test to assess selective visual attention. The subjects were asked to search for the target stimulus among non-targets as quickly as possible and to cancel out as many targets as possible within 4 min and 40 s. Performance score was calculated by subtracting

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commission errors from the number of correctly cancelled items.

Divided attention was tested by administering the subtest 'Divided attention' (TAP), i.e. a dual-task paradigm. This task requires attending to visual and acoustic stimuli simultaneously. Performance was measured by obtaining the mean reaction time for target present trials.

Memory

Verbal short-term memory was assessed using the 'Digit span forward' of the revised German version of the Wechsler Memory Scale (WMS-R; Wechsler, 2000). Subjects were required to repeat increasing strings of single digits in the order as given by the examiner. The number of correctly reproduced sequences was used as the test score.

'Digit span backward' (WMS-R) was used to assess verbal working memory performance. The number of correctly reproduced sequences in backward order was used as test score.

Free reproduction of two stories read aloud by the examiner, each containing 25 items ('Logical memory'; WMS-R), was used to test immediate and delayed verbal recall. The number of correct reproduced items was used as the performance measure.

Executive functions

Cognitive flexibility was tested by simple and alternate verbal fluency tasks ('Regensburger Wortflüssigkeits-Test'; Aschenbrenner *et al*. 2000). In each subtest, subjects are required to produce as many words as possible: (1) beginning with a particular initial letter; (2) belonging to a specific semantic category; (3) alternating between words with a particular initial letter; and (4) alternating between semantic categories within 2 min each. The number of valid responses was calculated, excluding repetitions and intrusion errors.

The Raven Standard Progressive Matrices (SPM) test (Raven *et al*. 1988) was used to test visual problem solving. Its five subtests contain 12 items each, which are marked by different levels of complexity. The number of correctly solved items served as a measure of visual problem-solving ability.

Three subtests of the Cambridge Neuropsychological Test Automated Battery (1999; CeNeS Pharmaceuticals plc, Cambridge, UK), namely Delayed Matching to Sample (DMS), Intradimensional/Extradimensional Attentional Set Shifting (ID/ED) and Spatial Working Memory (SWM) were used to assess working memory and cognitive flexibility.

In the 'DMS' task, subjects were confronted with a complex abstract pattern and then asked to identify this pattern in a selection of four similar stimuli. This selection was presented after 0, 4 or 12 s in a random order. The number of correct identifications at each condition was used as the test score.

The 'ID/ED' task involves nine visual discrimination levels, with subjects proceeding to the next stage once a criterion of six consecutive correct responses had been attained. The critical test conditions involve novel stimuli and subjects had to learn new examples which belong to the same dimension (ID shift). Then, the rule was reversed so that the previously learned shape becomes irrelevant (ED shift). Thus, the ability to inhibit a previously learned rule and adopt a new rule by shifting attention from one dimension to another was tested.

In the 'SWM' task, subjects were required to search for tokens hidden in a spatial array of boxes. The number of boxes increased from four to six to eight. A strategy score was derived from the number of search sequences which were started with the same box.

All tests were administered also at follow-up, except three cognitive tasks ('Aufmerksamkeits-Belastungstest d2', Logical memory and Raven SPM test) for practicability reasons.

Statistical analyses

Statistical analyses included paired-sample *t* tests and McNemar's test for assessing change in psychopathology and cognitive function, and independent *t* tests and χ^2 tests for comparing age, education and gender between groups. To control for possible effects of medication on cognitive performance, we pooled sedative drugs (tricyclic antidepressants, Mirtazapine) and non-sedative drugs (selective serotonin re-uptake inhibitors, noradrenergic and specific serotonergic antidepressants, selective noradrenaline re-uptake inhibitors, monoamine oxidase inhibitors). Analyses of covariance (ANCOVAs) controlling for age, gender, type of medication (sedative antidepressants, non-sedative antidepressants, use of benzodiazepines, neuroleptic treatment) and education were used to detect differences in the cognitive performance between remitting and non-remitting patients and between patients with a first depressive episode and recurrent depression. Change scores in cognitive performance between admission and discharge were computed as regression residuals controlling for baseline values. In addition, non-parametric Mann–Whitney *U* tests using regression residuals of the cognitive tests corrected for the same covariates as in the ANCOVAs were applied for analysing differences between diagnostic subgroups and for patients with follow-up data. Multiple regression analyses were

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applied to determine practice effects, considering age, gender and education as possible confounding variables. Effect sizes were computed as Cohen's d for t tests and Cohen's f for ANCOVAs. Partial correlations, controlling for age, gender, type of medication and education, were used to determine relationships between cognitive function and severity of depression.

The level of significance was set to $p = 0.05$ (two-tailed). No correction for the number of neuropsychological tests was applied to avoid a disproportional loss of power, as the different tests display highly interrelated facets of the same phenotype of cognitive performance. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

All patients fulfilled the DSM-IV criteria for a major or recurrent unipolar depression. Seven patients had psychotic features. The average hospitalization time was 9.3 weeks (S.D. = 4.8 weeks). Remission of depression was defined by a HAMD score of $\leqslant 9$ prior to discharge. According to this criterion, 43 patients were assessed as remitted and 10 as not remitted at discharge. The analysis of change in symptom severity revealed a significant reduction of the HAMD score [25.1, S.D. = 5.1 on admission and 6.3, S.D. = 5.1 at discharge; $t(52) = 19.15$, $p < 0.001$].

Follow-up assessments were available in 20 remitted patients; seven of them (five female, two male; mean age 44.1, S.D. = 10.2 years) suffered a relapse and 13 (five female, eight male; mean age 40.3, S.D. = 4.7 years) remained in remission.

Cognitive functions

Impaired cognitive performance was defined as having a test score that is more than one standard deviation below the mean score of the normative samples according to age and gender.

Table 2 displays the results of cognitive assessments for patients and controls.

Patients were impaired in all cognitive domains (information processing/attention, memory, and executive functions) on admission as well as at discharge. Significant improvements were found for 10 (immediate and delayed recall, letter cancellation, trail-making test, DMS with 4 and 12 s delay, SWM strategy score, semantic and phonological verbal fluency, and the Raven SPM test) of 25 cognitive tests.

Cognitive improvement after correcting for practice effects

We observed significant practice effects in the control group for immediate and delayed recall, letter cancellation, trail-making test, semantic flexibility, and the Raven SPM test. Patients showed improvements in five of these cognitive tests, which may at least partly result from practice rather than treatment effects, with the exception of semantic flexibility where only control subjects improved significantly (see Table 2).

To correct for practice effects, we evaluated the effects of test repetition in the control group with respect to baseline performance, age, gender and education by multiple regression. We reanalysed changes in patients' performance in these five cognitive tests with residuals of the test performance at discharge corrected for the practice effects observed in controls. The ANCOVAs did not reveal significant improvement in all five tests after controlling for practice effects (all $p > 0.05$). Thus, cognitive improvement in patients seems to be confined only to those five tests unbiased by practice (DMS with 4 and 12 s delay, SWM strategy score, semantic and phonological verbal fluency).

Impairment rates

The frequency (%) of patients with impaired cognitive performance is shown in Table 3. We observed a significant decrease in the number of impaired patients in six cognitive tests (immediate and delayed recall, letter cancellation, alertness +, DMS 4 s, and SWM strategy). The highest rate of impairment was found in the 'ID/ED' task, which predominantly requires executive functions. More than half of patients (56.6%) also showed impaired performance in the alertness task on admission. This rate decreased to 39.6% at discharge, indicating that only about 15% of patients improved while the majority of patients were impaired in alertness.

Cognitive functions and course of depression

For investigating the relationship between cognitive deficits and remission of depression, an ANCOVA was computed to determine whether the independent variable (reaching remission or not) was related to cognitive performance on admission. We found no significant differences between remitters and non-remitters (all $p > 0.05$). Thus, no cognitive function could be identified to serve as a predictor for the course of depression between admission and discharge.

To further examine associations between cognitive function and psychopathological outcome, 20 patients who were remitted at discharge were re-examined about 6 months later; seven patients suffered a relapse while 13 patients were still remitted. ANCOVA controlling for age, gender, education and medication

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Table 2. *Results of cognitive assessment for patients (n = 53) and controls (n = 13)*

	Patients					Controls				
Cognitive tests	Admission	Discharge	$F(1, 47)$[a]	p	Effect size f	First examination	Second examination	$t(12)$	p	Effect size d
Memory										
Digit span forward	7.38 (2.06)	7.55 (1.83)	1.12	N.S.	0.15	8.54 (1.76)	8.54 (1.66)	0.00	N.S.	0.00
Block span forward	7.83 (1.71)	8.40 (1.69)	3.16	N.S.	0.26	9.15 (1.07)	8.85 (1.41)	1.00	N.S.	0.24
Immediate recall	26.62 (5.97)	30.81 (6.31)	22.35	<0.001	0.69	30.54 (4.98)	33.85 (5.70)	−3.07	0.010	0.62
Delayed recall	22.15 (6.64)	28.45 (6.17)	39.95	<0.001	0.92	26.92 (7.29)	31.00 (6.70)	−3.12	0.009	0.58
Attention										
Letter cancellation	148.25 (34.96)	171.98 (37.66)	45.44	<0.001	0.98	156.62 (39.38)	176.15 (36.49)	−6.56	<0.001	0.51
Trail-making test	87.21 (24.04)	77.50 (21.06)	4.06	0.050	0.29	79.81 (17.52)	68.54 (13.35)	6.35	<0.001	0.72
Alertness +	276.62 (54.23)	268.87 (54.86)	1.50	N.S.	0.18	245.65 (35.37)	242.88 (26.89)	0.35	N.S.	0.09
Alertness −	281.50 (55.93)	274.23 (52.60)	1.64	N.S.	0.19	250.08 (33.91)	245.38 (29.69)	0.90	N.S.	0.15
Divided attention	698.01 (114.47)	680.81 (79.06)	2.47	N.S.	0.23	641.50 (68.07)	654.46 (44.70)	−0.84	N.S.	0.23
Executive functions										
DMS simultaneous	9.60 (0.69)	9.60 (0.60)	0.76	N.S.	0.13	9.77 (0.60)	9.85 (0.38)	−0.37	N.S.	0.16
DMS 4 s	8.81 (1.19)	8.91 (1.26)	4.12	0.048	0.29	9.46 (0.97)	9.38 (0.77)	0.23	N.S.	0.09
DMS 12 s	7.49 (1.72)	7.72 (1.78)	4.46	0.040	0.31	8.23 (1.30)	8.69 (0.95)	−1.20	N.S.	0.40
SWM four boxes	1.26 (1.96)	1.11 (1.79)	0.43	N.S.	0.10	0.69 (1.18)	0.46 (0.97)	0.51	N.S.	0.21
SWM six boxes	8.06 (7.52)	6.75 (6.67)	3.21	N.S.	0.26	3.15 (3.98)	2.92 (4.39)	0.22	N.S.	0.05
SWM eight boxes	17.57 (12.21)	17.09 (11.56)	0.89	N.S.	0.14	13.77 (12.01)	12.54 (8.98)	0.50	N.S.	0.12
SWM strategy	34.13 (6.06)	32.94 (4.92)	4.74	0.035	0.32	32.54 (5.13)	32.08 (4.73)	0.57	N.S.	0.09
Digit span backward	6.32 (1.85)	6.19 (2.11)	0.03	N.S.	0.03	6.77 (2.13)	7.38 (2.18)	−1.60	N.S.	0.28
Block span backward	7.89 (1.72)	7.81 (1.93)	0.00	N.S.	0.00	9.69 (1.03)	9.46 (1.61)	1.00	N.S.	0.17
ID/ED stages	8.09 (1.29)	8.13 (0.98)	2.48	N.S.	0.23	8.38 (0.96)	8.62 (0.77)	−0.82	N.S.	0.28
ID/ED total	94.19 (23.89)	92.36 (20.56)	2.32	N.S.	0.22	81.77 (15.17)	76.69 (23.31)	0.96	N.S.	0.26
Semantic verbal fluency	38.85 (10.48)	40.85 (9.10)	5.81	0.020	0.35	39.92 (6.80)	39.00 (6.30)	0.48	N.S.	0.14
Phonological verbal fluency	25.26 (8.10)	28.15 (9.24)	4.41	0.041	0.31	26.62 (5.65)	29.23 (5.79)	−1.30	N.S.	0.46
Semantic flexibility	24.94 (4.63)	26.36 (5.23)	1.07	N.S.	0.15	23.31 (2.90)	26.85 (5.24)	−3.59	0.004	0.84
Phonological flexibility	23.04 (6.41)	24.94 (6.75)	3.14	N.S.	0.26	24.23 (2.92)	25.62 (5.12)	−1.16	N.S.	0.33
Raven SPM test	43.55 (8.74)	45.66 (7.27)	10.99	0.002	0.48	44.23 (6.50)	47.62 (5.94)	−3.33	0.006	0.54

N.S., Non-significant; DMS, Delayed Matching to Sample; SWM, Spatial Working Memory; ID/ED, Intradimensional/Extradimensional Attentional Set Shifting; SPM, Standard Progressive Matrices.

Values are given as mean (standard deviation).

[a] Controlled for sedative antidepressants, non-sedative antidepressants, benzodiazepines, neuroleptic treatment, and mood stabilizers.

Table 3. *Percentage of patients with impaired cognitive performance on admission and at discharge* ($n = 53$)

Cognitive tests	Admission	Discharge	p
Memory			
Digit span forward	30.2	22.6	N.S.
Block span forward	28.3	20.8	N.S.
Immediate recall	22.6	7.5	0.021
Delayed recall	37.7	5.7	<0.001
Attention			
Letter cancellation	24.5	5.7	0.006
Trail-making test	22.6	13.2	N.S.
Alertness +	56.6	39.6	0.049
Alertness −	49.1	39.6	N.S.
Divided attention	41.5	47.2	N.S.
Executive functions			
DMS simultaneous	1.9	0.0	N.S.
DMS 4 s	41.5	24.5	0.049
DMS 12 s	49.1	43.4	N.S.
SWM four boxes	22.6	20.8	N.S.
SWM six boxes	30.2	22.6	N.S.
SWM eight boxes	30.2	28.3	N.S.
SWM strategy	43.4	26.4	0.035
Digit span backward	34.0	45.3	N.S.
Block span backward	17.0	34.0	N.S.
ID/ED stages	39.6	41.5	N.S.
ID/ED total	60.4	56.6	N.S.
Semantic verbal fluency	17.0	9.4	N.S.
Phonological verbal fluency	18.9	13.2	N.S.
Semantic flexibility	11.3	7.5	N.S.
Phonological flexibility	34.0	24.5	N.S.
Raven SPM test	1.9	0.0	N.S.

N.S., Non-significant; DMS, Delayed Matching to Sample; SWM, Spatial Working Memory; ID/ED, Intradimensional/Extradimensional Attentional Set Shifting; SPM, Standard Progressive Matrices.

revealed no significant differences between the two groups at discharge (all $p > 0.05$). The only significant difference was found for alertness, where relapsed patients performed significantly poorer at follow-up [277.79, S.D. = 16.5 *versus* 239.08, S.D. = 23.0; $F(1, 11) = 7.07$, $p = 0.02$]. Considering the small and uneven sample size of the two groups, we reanalysed the data with a non-parametric Mann–Whitney U test using regression residuals of alertness corrected for the same covariates as in the ANCOVA. We replicated the finding of a worse alertness performance in relapsed patients at follow-up (Mann–Whitney $U = 16.0$, $p = 0.019$).

Regarding the rate of impaired patients, there was no significant reduction in any test between discharge and follow-up (Table 4).

Partial correlations did not reveal any significant correlation between cognitive function and severity of depression, except for a weak association between cognitive performance in the SWM test (six-box condition) and HAMD score on admission ($r = -0.34$, $p = 0.02$). This single correlation was no longer present at discharge. Furthermore, cognitive test results did not significantly differ between patients suffering from a first episode and those with recurrent depression, either on admission or at discharge (all $p > 0.05$).

In addition, we compared cognitive performance between patients with and without psychotic symptoms by applying the Mann–Whitney U test using regression residuals of the cognitive tests corrected for the same covariates as in previous analyses. The only differences were found for 'DMS' (4 s delay), where patients without psychotic symptoms showed a better performance (mean psychotic: 7.71, S.D. = 1.50, mean non-psychotic: 8.98, S.D. = 1.06; Mann–Whitney $U = 75.0$, $p = 0.022$), and in 'Digit span backward', with a better performance of patients with psychotic symptoms (mean psychotic: 8.0, S.D. = 1.53, mean

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Table 4. *Percentage of patients with impaired cognitive performance at discharge and follow-up* ($n=20$)

Cognitive tests	Discharge	Follow-up	p
Memory			
Digit span forward	15	10	N.S.
Block span forward	5	5	N.S.
Attention			
Trail-making test	5	0	N.S.
Alertness +	35	15	N.S.
Alertness −	25	30	N.S.
Divided attention	40	25	N.S.
Executive functions			
DMS simultaneous	0	0	N.S.
DMS 4 s	10	30	N.S.
DMS 12 s	25	30	N.S.
SWM four boxes	25	10	N.S.
SWM six boxes	25	25	N.S.
SWM eight boxes	25	20	N.S.
SWM strategy	20	25	N.S.
Digit span backward	35	10	N.S.
Block span backward	30	10	N.S.
ID/ED stages	15	25	N.S.
ID/ED total	35	25	N.S.
Semantic verbal fluency	5	10	N.S.
Phonological verbal fluency	5	20	N.S.
Semantic flexibility	0	0	N.S.
Phonological flexibility	15	10	N.S.

N.S., Non-significant; DMS, Delayed Matching to Sample; SWM, Spatial Working Memory; ID/ED, Intra-dimensional/Extradimensional Attentional Set Shifting.

non-psychotic: 6.07, S.D. = 1.77; Mann–Whitney $U=81.0$, $p=0.035$). There was no significant difference at discharge in any test performance (all $p>0.05$).

Discussion

As reported by other authors (Austin *et al*. 2001; Stordal *et al*. 2004; Neu *et al*. 2005), we found impairments in information processing/attention, memory, and executive functions in patients with acute depression. After remission, performance improved in some cognitive tests but was still impaired in a high proportion of patients (up to 57%). There were no significant differences in cognitive performance between remitted and non-remitted patients. Furthermore, among 25 cognitive measures, only one measure was correlated with depression severity, indicating a dissociation between cognitive function and psychopathological symptoms. This observation is consistent with previous findings (Degl'Innocenti *et al*. 1998; Fossati *et al*. 1999; Majer *et al*. 2004; Bearden *et al*. 2006). Thus, we suggest a core cognitive dysfunction which exists independently of psychopathological status. Further evidence for this assumption stems from the absence of any significant reduction of the number of impaired patients between discharge and follow-up. Impairments were found in all cognitive domains we assessed, indicating a non-specific deficit pattern. Our data do not confirm a predominance of executive or memory deficits as suggested by others (e.g. Veiel, 1997; Fossati *et al*. 1999; Sweeney *et al*. 2000). Our results suggest a generalized, unspecific impairment profile rather than the existence of selective impairments in specific cognitive domains. However, a high number of patients were impaired in basic attentional tasks (e.g. 56.6% in alertness). These attentional deficits might be responsible for impairments in other cognitive domains, since attention, memory, and executive functions are interrelated cognitive processes (Lezak *et al*. 2004). If a sufficient attentional level cannot be reached or maintained, a global, unspecific reduction of performance in all cognitive domains may result. Furthermore, attentional functions depending on executive control, e.g. selective and divided attention, may particularly affect cognitive capacities that depend crucially on these attentional functions (e.g. Cohen & O'Donnell, 1993; Mialet *et al*. 1996; Zihl *et al*. 1998). Although impaired attention is a core symptom of depression, detailed empirical evidence on this issue is, unfortunately, still limited. Taken together, these results support the hypothesis that cognitive dysfunction represents a trait marker rather than simply being an epiphenomenon of acute depression (Austin *et al*. 2001; Reppermund *et al*. 2007). In addition, our data support the final common pathway disorder hypothesis (Mialet *et al*. 1996; Zihl. *et al*. 1998). Seen from this neurobiological viewpoint, cognitive impairment results from any type of dysfunction of the underlying network(s), irrespective of whether it is caused by morphological, physiological or biochemical alterations.

Although evidence on the neuropathology of depression is still preliminary, it is rather likely that functional or even morphological changes contribute to the dysfunction of the neural networks that regulate mood and associated cognitions; in depression, these changes have been observed particularly in the prefrontal brain (Harrison, 2002). However, our observations of the dissociation between affective and cognitive symptoms underline the importance of distinguishing between different, regional frontal subsyndromes. By referring to Duffy & Campbell (1994), we suggest that the main functional networks affected in depression are those subserving executive function in cognition ('dorsal convexity system'), and motivation and emotion ('mesial frontal system'). Because

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of the dissociation between cognitive impairments and psychopathological symptoms, one might speculate whether subtypes of depression exist, which can be described as follows: (i) presence of severe psychopathological symptoms with only mild cognitive deficits; (ii) cognitive symptoms with only mild to moderate psychopathological symptoms; and (iii) a combination of severe depressive symptoms and cognitive dysfunction. These subtypes correspond to the apathetic mesial frontal syndrome, the dysexecutive dorsal convexity syndrome, and a combination of both.

In contrast to Majer *et al*. (2004) and Weiland-Fiedler *et al*. (2004) we did not find a relationship between cognitive function and further course of depression. In addition, we did not find significant differences between remitters and non-remitters nor between patients suffering a relapse and those who remained in remission 6 months after discharge. Differences across studies regarding patients' characteristics, age, gender, education, treatment settings and the consideration of practice effects may account for these inconsistent findings. Our findings demonstrated the importance to consider practice effects in neuropsychological studies. In one-quarter of the tests we administered, we identified practice effects. However, due to the small sample size of our control sample, the results concerning practice effects should be carefully interpreted; further studies are required to investigate practice effects in larger samples.

There is still no uniform explanation for the occurrence and persistence of cognitive impairments in affective disorders. Depression can be accompanied by a variety of neurobiological alterations; it is, therefore, unlikely that one factor alone causes cognitive impairment. Cognitive deficits have been linked, for example, to hypometabolism in specific brain areas, in particular within the prefrontal cortex (Bench *et al*. 1993), to hypercortisolaemia (Bremner *et al*. 2004), and to dysfunctional interactions of the serotonergic system and the hypothalamic–pituitary–adrenocortical system (McAllister-Williams *et al*. 1998). Egeland *et al*. (2005) and Gomez *et al*. (2006) reported that higher cortisol levels are associated with deficits in executive function and memory whereas processing speed is associated with severity of depressive symptoms. These observations indicate differential effects of cortisol and psychopathology on cognition: hypercortisolism may affect complex cognitive capacities whereas the influence of affective symptoms on cognition may be restricted to 'low-level' functioning. In summary, different subtypes of depression might exist which share a particular pattern of psychopathological symptoms but differ with respect to the presence and severity of cognitive impairments, and neurobiological (Nestler *et al*. 2002) and genetic (Goldberg, 2006) features. Combining neuropsychological assessments, functional brain imaging and neuroendocrine measures might be a promising strategy for illuminating the neurobiological correlates of the occurrence and persistence of cognitive impairments.

One limitation of the present study is that all patients were under medication during neuropsychological assessments, which might have influenced the results. We have tried to cope with this limitation by including the types of medication as covariates. Yet, since the first cognitive assessment was carried out 3–10 days following admission, an adjustment of treatment and dosage might have influenced the results.

Many studies have shown that the impact of antidepressants on cognitive performance may be marginal or non-existent (Podewils & Lyketsos, 2002; Ferguson *et al*. 2003; Siepmann *et al*. 2003). A recent treatment study with sertraline demonstrated that the effect of antidepressant treatment alleviated psychomotor slowing and was beneficial with respect to executive functions (Constant *et al*. 2005). Nevertheless, it is important to replicate our results in medication-free patients. Porter *et al*. (2003) examined depressed patients who had been drug-free for at least 6 weeks. In comparison with healthy controls, patients were impaired in attention, memory, and executive functions. In a follow-up investigation 2 to 6 months after the first assessment, reduced psychomotor dysfunctions and greater improvement in verbal memory were observed in remitted compared with non-remitted patients (Gallagher *et al*. 2007). In line with our findings, these studies demonstrate that cognitive impairments are not (or at least not completely) secondary to the effects of medication.

Moreover, it has been suggested that ruminative thoughts could be at least partly responsible for cognitive impairments (Hertel, 1998; Watkins & Brown, 2002). However, cognitive deficits are still existent in the remitted state of depression where rumination is no longer present.

A further limitation is that our sample consisted of moderately to severely depressed, middle-aged in-patients. Thus, the results cannot be generalized to other subgroups such as mildly depressed out-patients or geriatric patients. There is evidence suggesting that hospitalized patients have more pronounced cognitive deficits (Christensen *et al*. 1997). However, we found an association between cognitive performance and severity of depression for only one cognitive measure.

Cognitive deficits affect not only everyday life activities but also the patient's ability to work and they also delay re-employment. As a clinical implication, it is thus important to consider additional

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neuropsychological treatment. In patients suffering from schizophrenia it has been shown that systematic neuropsychological training leads to improvement in cognitive functioning and, as a consequence, to higher social competence and self-confidence (Sartory *et al*. 2005). In combination with pharmacological treatment and psychotherapy, this approach may help to prevent relapses.

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Declaration of Interest

None.

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