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F.M. Reischies · P. Neu

Comorbidity of mild cognitive disorder and depression – a neuropsychological analysis

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Abstract Mild cognitive impairment is found in many cases of depression, and it is mostly assumed to improve during the time course of depression remission.

Recent data question the reversibility of low cognitive test performance in depression. The aim of this study is to determine the degree of reversibility and the proportion of patients who will not demonstrate reversibility of cognitive dysfunction.

Consecutive inpatients suffering from depression (N=102) were investigated and N=82 matched control subjects. N=57 of the patients were diagnosed as major depression according to DSM-IV. A total of N=67 could be retested after remission of depression (N=32 of the patients with major depression) and a matched control group (N=62). Neuropsychological tests were applied in a test session which avoids the effects of fatigue in the patients by the short duration of strenuous tests.

For most neuropsychological tests an impaired performance in the depressed patients was found. About one third of the depression subjects performed at an impaired level in tests of averbal memory and verbal fluency (below 5th percentile). In the follow-up investigation, a slight improvement in performance could be assessed for both the depression and the control group, which was, however, attributed to a general test training effect. No normalization of cognitive test performance was found in spite of complete recovery of the affective symptoms. No correlation between the duration of the disease before the index episode or number of episodes and cognitive deficits could be found.

The data of the neuropsychological deficits of depressed patients, which are stable in the time course of the affective disorder, may indicate that these patients may suffer from comorbidity of both depression and mild cognitive disorder. The findings are discussed as 1) indicating only a minor impact of the depressed mood on the cognitive performance and 2) they are consistent with a role of brain lesions which have been reported in several studies in a subgroup of depression.

Key words Cognitive deficits · Comorbidity · Antidepressant drugs · Longitudinal study · Controlled study

Priv. Doz. Dr. Friedel M. Reischies (✉) · Dr. P. Neu
Psychiatrische Klinik der Freien Universität Berlin
Eschenallee 3, D-14050 Berlin, Germany
e-mail: reischie@zedat.fu-berlin.de

Introduction

The question, whether cognitive deficits in depression are reversible with remission of depression, is crucial for some of the neuroscience models of depression which are at this time being discussed in depression research. One of the models is that of hippocampal damage occurring in the time course of depressive episodes (Sapolsky et al. 1996, Sheline et al. 1996, Kessing 1998); it predicts a deficit of episodic memory in depressed subjects, which should be persistent or even progressive, as well as a relation to a) the duration of the disease and b) number of depressive episodes or both.

The second model is that of subcortical and basal ganglia lesions, reported in magnetic resonance imaging (MRI), which are considered as causal for depression or at least as crucial vulnerability factors for depression, i. e., there may be a role in the pathogenesis of the depressive syndrome (Brown et al. 1992, Rabins et al. 1991, Fujikawa et al. 1996, Greenwald et al. 1996, Alexopoulos et al. 1997). Several studies have demonstrated brain imaging findings of white matter and basal ganglia lesions in depression for patients who are 45 years of age and older. This lesion model would predict – at least for a subgroup of depressed patients – a cognitive impairment which is not reversible, i. e., which will persist with the remission of affective symptoms (Zubenko et al. 1990). The issue of reversibility of cognitive deficits in depression is related to the long-standing topic of depressive pseudodementia, on the one hand, and comorbidity of depression and brain lesions as well as comorbidity of depression and dementing illness, on the other hand, which are diagnostic problems

that occur mostly in late adulthood and old age (Caine 1981, Emery et al. 1992, Devanand et al. 1996).

Studies of cognitive performance in depression and of the time course of cognitive dysfunctions during remission of affective symptoms have shown controversial results (Burt et al. 1995, Christensen et al. 1997). First, some cognitive domains – especially recall of episodic memory and speeded retrieval from semantic memory – seem to be regularly impaired in depression (Cronholm et al. 1961, Calev et al. 1989, Caine et al. 1986). Some researchers could not identify deficits in distinct dimensions of cognitive and memory functions, for example, in the storage of episodic memory (Cronholm et al. 1961, Sternberg et al. 1976). The data about cognitive impairment in the literature are inconsistent for a number of reasons. It is not entirely clear whether depressed subjects have cognitive deficits at all; in this respect some researchers (Friedman et al. 1964) have put emphasis on proper control groups. Therefore, the selection of tasks and control subjects is important for the degree of impairment in test performance which can be found in depression. In this study a large group of depressed inpatients is compared with a properly matched control group on tests which are expected to demonstrate a deficit in the depressed subjects.

Second, if at least some depressed patients have deficits in performance on certain neuropsychological tests, there are, however, controversial findings with regard to reversibility (Burt et al. 1995, Reischies 1988). Some authors report improvement of cognitive performance after remission from depression, others do not. This may be explained by a number of reasons, namely the influence of fatigue during the testing session has been discussed as a possible reason for a more pronounced deficit in depression (Whitehead 1973) and furthermore a reduction in the maintenance of vigilance has been described (Byrne 1977, Malone et al. 1977). Effects of exhaustion and tiredness of depressed patients are potential non-cognitive confounders in longitudinal studies. The application of strenuous tests of long duration might lead to an artifact, because in remission of affective symptoms tiredness and exhaustion are improved and as a result of that also the cognitive test performance. In that case, the improved test performance in remission of affective symptoms may be explained by non-cognitive effects. In order to minimize this source of artifact, this study put emphasis on the short duration of the total test session and especially of strenuous tasks.

Methods

Consecutively admitted, depressed inpatients (N=186) were checked, whether they fulfilled the inclusion criteria: DSM-IV (APA 1987) criteria for an episode of major depression; bipolar affective disorder, depressed; or schizoaffective psychosis, depressed. Exclusion criteria were major sensory loss, confusional syndrome (or delirium) or intoxication. The depressed subjects must be native speakers of the German language because of the verbal tests. 117 subjects passed the criteria, but 8 refused to participate in the test session and for 7 patients a different diagnosis was finally given so that they had to be excluded from the sample. 102 depression cases were analysed, 57 of them in an episode of major depression according to DSM-IV. The age, sex, and education data as well as the severity of depression assessed by the Bech Rafaelsen Melancholia Scale (BRMS, Bech et al. 1980) are shown in Table 1. A group of healthy volunteers (control group N=82) was examined and N=62 were tested twice using the same test battery. The control subjects were without any psychiatric or neurological diseases and were not taking any psychotropic drugs. Both groups – patients and controls – were well matched by age, sex, school education and socioeconomic status (see Table 1).

The tests were selected using two criteria: 1) The total testing time should be short; therefore, tests of short duration of performance, which are reliably used in clinical neuropsychology, were used. 2) Those major neuropsychological domains, which are expected to demonstrate reversible performance deficits in depression, should be assessed. The test session included

- the *RAVLT Test* (Lezak 1995), a 15-word learning task which was repeatedly (two times) read to the subject. Learning trials 1 and 2 as well as the delayed recall at the end of the session were used as parameters for episodic memory (short-term memory). The test proved to be valid in other studies on depression (Brand et al. 1992).
- Non-verbal memory was investigated by the *visual memory subtest of the Wechsler Memory Scale* (Wechsler 1945), which is validated for figural short-term memory.
- Furthermore, in order to assess a severe memory problem (as in a dementia syndrome), the 10 *orientation items of the MMSE examination* (Folstein et al. 1975, Walzer et al. 1997) were applied. These items were used as a control test for major memory problems which occur regularly in dementia. A disorder of temporal orientation is rarely found in depression and accordingly no improvement of test performance could be expected.
- *Verbal fluency* was measured by the animal fluency task. The subject is asked to name as many animals as possible in 1.5 min.

Table 1 Depression and control groups – the number of subjects tested at time 1 and of those retested at time 2 is given together with sociobiographic and depression data. (major depression: MD, Bech Raffaelsen Melancholia Scale: BRMS)

	MD		**Depression non MD**		**Depression total group**		**Control group**
	t1	**t1 and t2**	**t1**	**t1 and t2**	**t1**	**t1 and t2**	
N	57	34	45	37	102	67	82
age (yrs)	53.70 (11.40)	54.35 (11.69)	49.6 (10.36)	49.73 (10.12)	51.89 (11.09)	51.71 (11.14)	52.30 (10.74)
gender f/m (%)	73.7/26.3	73.5/26.5	66.7/33.3	62.2/37.8	70.6/29.4	67.2/32.8	70.7/29.3
education(yrs)	10.10 (1.44)	10.08 (1.46)	10.48 (1.79)	10.54 (1.80)	10.27 (1.16)	10.32 (1.65)	10.30 (1.53)
Depression BRMS	18.56 (4.37)	t1: 19.32 (4.59) t2: 4.61 (2.16)	20.53 (5.31)	t1: 19.94 (5.33) t2: 3.89 (2.75)	19.43 (4.88)	t1: 19.70 (4.70) t2: 4.29 (2.47)	

- *The Reitan Trailmaking Test-A* (Reitan 1958) was included in the test battery as a valid and commonly applied test for psychomotor speed. In this test a connecting line is to be drawn as rapidly as possible for 25 numbers in ascending sequence.

For all tests, except the WMS visual memory and Reitan Trailmaking Test-A, parallel forms were used at the retest. The test session was short and lasted less than 15 min in order not to risk premature fatigue of the depressed subjects.

The patients were investigated within the first three days after admission to the inpatient treatment facility. Several patients were without medication or medication was discontinued (N=23) and no new medication was given until testing had taken place. The retest sample consists of 77 patients (sociobiographic data and BRMS rating at remission see Table 1); 15 subjects refused the retests, 9 could not be retested for various reasons and 1 patient had committed suicide. The retests were performed individually at remission of depression at the end of inpatient treatment.

Results

Performance at initial investigation

The group of depressed patients had a lower test performance compared with that of the control group. The group comparison is statistically significant for all tests (t-test, $p< 0.001$, Table 2) – with the exception of the orientation test, where no statistical significance was found and which demonstrates, as expected, a ceiling effect. The calculation of the effect size reveals that the difference in test performance is of a magnitude of 1/2 to 1 standard deviation. There is no large variance of the effect size between the tests. The subgroup of patients with major depression according to DSM-IV demonstrated only slightly more impairment compared with the rest of the depression cases (not statistically significant, see Table 2).

In order to answer the question of how many depressed patients have impaired test performance, we calculated a fifth percentile for the control group for the tests. The number and percentage of major depression subjects, who fell below this cut off value are given in Table 3. The highest number of major depression subjects below this cut off were found in verbal fluency and visual memory, but not in the RAVLT test. The number of depressed patients with 1 or more errors on the orientation task was higher (n=18; 17.6 %) compared to that of the control group (n=4; 4.9 %), Chi-square (df=1) was 7.04 ($p< 0.01$). The same is true for the major depression episode (DSM-IV) subgroup (10 of 57, 17.5 %, Chi-square (df=1) 5.96, $p< 0.05$). The exact number of impaired subjects, however, cannot be estimated because of the ceiling effect.

Longitudinal data

In the follow-up investigation, the test performance of the depressed subjects improved only to a small extent in most of the tests. A mild improvement of the same magnitude, however, was found in the control group (see Table 4, Fig. 1). In a two-way repeated-measurement ANOVA with the factors time (initial investigation and follow-up) and diagnosis (depression and control), the interaction term (time * diagnosis) did not approach statistical significance for any single neuropsychological test, which can be seen in Fig. 1. The mean time interval between the two tests was 4.4 (sd 1.9) months (for controls 4.5, sd 1.6 months), which is often the case for inpatient treatment of depression in Germany.

An attempt was made to estimate the number of remitted patients suffering from a neuropsychological impairment by applying the cut off of the control group. The cut off was empirically derived by calculating the percentiles for the control group at the two testing times (see Table 3). There is no major shift in the cut off between the two test times. Approximately the same number of impaired depression patients was found at the follow-up investigation, compared with the initial testing.

Table 2 Test performance of the major depression (MD) and other depression groups compared with the control group

	Control n=82		**MD n=57**		**Depr. non MD n=55**		**Depr. n=102**		**Dep.vs.**
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	**Cont.**
RAVLT 1	7.38	1.63	5.86	1.91	6.13	1.50	5.98	1.74	1
RAVLT 2	9.75	1.88	8.19	2.51	8.40	2.19	8.28	2.36	1
RAVLT delayed recall	7.61	2.25	5.29	3.00	5.75	2.48	5.00	2.78	1
Trailmaking A (s)	31.79	11.92	48.83	23.33	40.77	14.43	45.28	20.21	1
Verbal Fluency 0–30 s	17.58	5.24	12.97	4.03	14.21	3.74	13.58	3.91	1
Verbal Fluency 31–60 s	8.25	3.23	6.44	3.81	5.79	2.79	6.11	3.34	1
Verbal Fluency 61–90 s	7.05	3.60	5.62	3.21	5.67	2.32	5.64	2.79	1
Visual Reproduction	9.83	2.95	6.59	3.51	7.73	3.49	7.09	3.53	1
MMSE Orientation	9.95	0.21	9.77	0.63	9.80	0.45	9.78	0.55	Chi square s. text

1) Total depression vs control; t-test, $p< 0.001$, Bonferroni $p< 0.05$

Table 3 Percentage of impaired test performance at the first testing and follow-up

Test	first test		follow-up test		Comment
	Cut off: 5th percentile of the control group	**Major depression: % performance below 5th percentile**	**Cut off: 5th percentile of the control group**	**Major depression at remission: % performance below 5th percentile**	
Wechsler MS Visual M	< 5	38.6	< 5	38.2	
Fluency Animals 90 s	< 17	36.8	< 17	32.4	
Reitan Trailmaking A	> 60	24.6	> 61	17.6	time of performance: 95-percentile
RAVLT Delayed Recall	< 5	15.8	< 5	14.7	
RAVLT 1st Trial	< 6	12.3	< 6	17.6	
RAVLT 2nd Trial	< 4	10.5	< 3	26.5	
Orientation Items MMSE	< 9	1.8	< 9	1.4	no normal distribution

Table 4 Follow-up investigation of major depression and a subgroup of matched control subjects

	Major Depression (unipolar) N=32		**Control N=32**		**main effect**		**Interaction**
	t1	**t2**	**t1**	**t2**	**diagn. (unip./ control)**	**time**	**time x diagn.**
	mean/SD	mean/SD	mean/SD	mean/SD	p	p	p
RAVLT 1	5.93/ 1.77	6.28/1.81	7.31/1.59	7.25/1.58	***	n. s.	n. s.
RAVLT 2	7.90/ 2.59	8.15/ 2.15	9.78/ 1.89	9.68/ 2.20	***	n. s.	n. s.
RAVLT delayed recall	4.96/ 2.96	5.25/ 2.24	7.58/ 2.54	7.84/ 2.59	***	n. s.	n. s.
Trailmaking A	47.34/21.59/	45.48/20.21	33.72/15.07	33.34/13.60	**	n. s.	n. s.
Verbal Fluency 0–30 s	12.90/ 4.14	13.55/ 4.66	18.90/ 5.49	18.37/ 5.78	***	n. s.	n. s.
Verbal Fluency 31–60 s	6.43/ 3.68	6.86/ 4.45	8.46/ 3.38	9.66/4.94	**	n. s.	n. s.
Verbal Fluency 61–90 s	5.37/ 2.94	5.31/ 3.28	9.12/ 3.12	8.03/ 3.40	**	n. s.	n. s.
Visual Reproduction	6.40/ 3.74	7.03/ 3.62	9.18/ 3.06	10.43/ 2.81	***	***	n. s.

n. s. p> 0.05, * p< 0.05, ** p< 0.01, ***p< 0.001

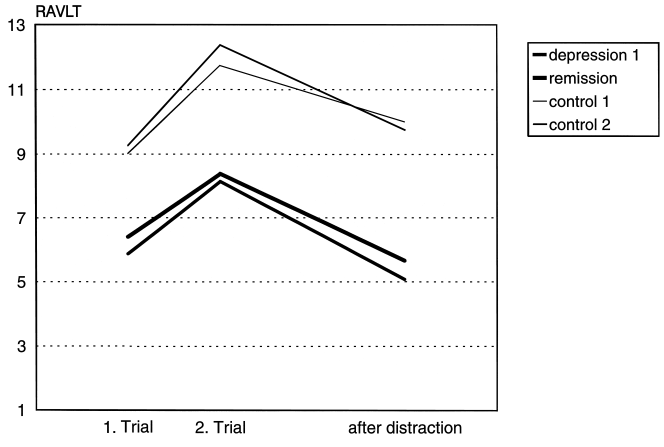

Fig. 1 Parallel improvement in the follow-up investigation for depressed subjects and the control group in the Rey Auditory Verbal Learning Test, recall trial 1 and 2 and delayed recall.

In order to analyse the change of test scores for the individual subjects, the result of the second test (t2; y axis) was plotted as dependent on the performance at the first test (t1; x axis). In case of an improvement of those depressed patients with impaired performance, a flatter slope would be expected, i. e., higher t2 values for low scoring depressed subjects at t1. However, no statistically significant difference in the slopes of the regression function for the major depression and the control group was found. Not even a subgroup of depressed subjects with a predominant improvement in cognitive performance could be identified. The individual subjects who performed low at the first test tended to perform low at the second test as well (for verbal fluency and RAVLT see Fig 2).

Medication effects: During depression a subset of patients (n=14 major depression episode, 5 bipolar and one dysthymia) was tested under stable antidepressant medication; this group could be compared with a matched group

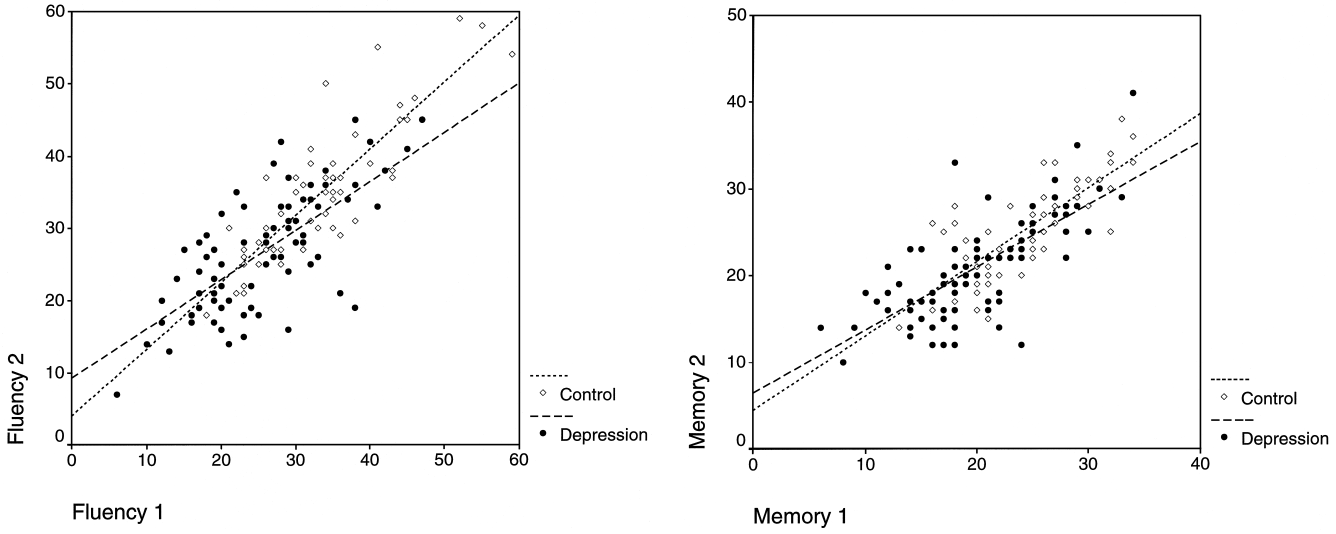

Fig. 2 The slope of the test performance of the animal fluency task (**a**) and RAVLT (sum of 2 trials, **b**) at time 2 related to the performance at time 1 for depression and remission of the patients and the follow-up investigation of the matched control subjects. Predominantly stable performance of depressed and remitted subjects can be found. No major improvement at time 2 is seen, especially not for low performing depressed patients, as expected.

Table 5 Comparison of medicated and non-medicated depressed subjects

	medicated		**non-medicated**		statistics
N	20		23		
BRMS	19.30	3.88	19.26	5.23	n. s.
RAVLT 1	5.75	1.86	6.04	1.77	n. s.
RAVLT 2	7.75	2.24	8.17	2.89	n. s.
RAVLT delayed recall	4.90	2.61	5.47	2.89	n. s.
Trailmaking A	50.88	17.01	45.24	24.39	n. s.
Verbal Fluency 90 sec.	24.50	9.33	23.21	7.17	n. s.
Visual Reproduction	6.55	3.10	6.21	3.02	n. s.

of depressed subjects who were not medicated at the time of the investigation (n=15 major depression episode, 5 bipolar, 2 dysthymia and 2 schizoaffective). The groups had the same age, education and severity of the depression syndrome. The comparison of medicated and non-medicated depressed subjects revealed no difference in test performance (Table 5). Medication consisted in most cases of tricyclic antidepressant drugs (amitriptyline, clomipramine and trimipramine 125 to 150 mg/pd). At the end of the inpatient treatment all patients had been treated with at least one antidepressant drug.

For the correlation analysis with respect to age, duration of the disease, number of episodes, and severity of the depression syndrome, a reduction of the number of statistical comparisons was achieved by a factor analysis of the neuropsychological test results. In this way we obtained the factor score of the first factor of a principal component analysis as one single variable representing the performance level of the subjects. First, the correlation between age and the neuropsychological performance factor was r=0.58 (t=–6.28, p< 0.001). A detailed analysis of this age correlation in the ANOVA did not show for any single test an interaction between age (± 55 yrs.) and diagnosis (depressive illness vs. control) that was statistically significant; this holds true with regard to the test performance and change in test score over time. Second, the duration of the depressive illness was not related to the neuropsychological performance factor (r=–0.08, n. s.). Third, the same turned out to be the case for the number of episodes of the illness (r=–0.03, n. s.). In a regression model only age but not the duration or number of episodes and not the interaction terms of both factors with age were statistically significant (age effect – standardised beta = –0.57, t=–3.69, p< 0.001). Fourth, only a correlation between the severity of the depressive syndrome (BRMS score) and the single test performance of the verbal fluency (r=0.36) at the first testing was found; but after Bonferroni correction for multiple comparisons, this correlation was not statistically significant.

Discussion

The results demonstrate a mild cognitive impairment for a considerable portion of a large sample of depressed inpatients – this holds true for the major depression episode cases as well as for the rest of the depression cases. About 20 to 38 % of the major depression episode patients performed below the 5 % level of the matched normal control group; if – due to the 5 percentile cut-off – the 5 % of the control group are subtracted, there remains a percentage of 15 to 33 % in the pathological group. Although there were no large differences between the neuropsychological tests, the number of impaired subjects was slightly more pronounced in averbal memory, psychomotor speed and verbal fluency.

The most important result is that no improvement of performance could be found at the time of remission of the affective symptoms up to the level of the control subjects. No statistically significant diagnosis-by-time interaction could be found, i. e., no group difference in the change in test performance. As seen in Fig. 1, depressed patients did not improve in their test performance within the time of improvement of affective symptoms to a greater extent than compared with the follow-up investigation of the healthy control subjects. Furthermore, about 20–25 % of the remitted subjects performed below the cut-off of the control group at their second testing. The finding seems to be especially valid because a representative clinical sample of depression patients was analysed.

It could be argued that the tests may not be sensitive to the detection of changes in cognitive functions. However, the Rey Auditory Verbal Learning Test (RAVLT) and Wechsler Memory Scale (WMS) visual memory are used in dementia research to demonstrate decline in performance (Bigler et al. 1989). The Reitan Trailmaking Test A (TMT) is sensitive with regard to monitoring improvement in patients with brain lesions (Eson et al. 1978). The RAVLT and Reitan TMT A are recommended for clinical neuropsychological investigation by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (1996). Therefore, an improvement in most tests could be expected – with the exception of the orientation task, in which only few errors were anticipated. A clear ceiling effect was found and therefore there are obvious problems of interpreting changes by means of this score.

Another possible concern is related to medication. If medication side effects are responsible for a persistent cognitive deficit in the patients, then a statistically significant difference between medicated and non-medicated subjects should have been found at the time of admission. Also an earlier study from our group did not find reliable medication effects on neuropsychological test performance in depression (Reischies 1993).

The reason why a number of studies of depressed subjects found some — mostly incomplete — recovery of cognitive function (see Abas et al. 1990, Burt et al. 1995, Christensen et al. 1997) must be discussed. The reasons might be (1) the size of the sample, (2) the follow-up investigation including the control subjects, and (3) the duration of the test session. (1) Mostly small samples of depressed subjects have been investigated in follow-up studies, so that the inclusion of several cases with depressive pseudodementia could have led to an improvement of mean performance in the depression group. (2) If an improvement of depressed patients within the time of treatment of depression is found, one must check a control group for a general test training effect. A degree of anxiety during the testing might be relieved at the second testing because the person knows the second time what is to be expected. Furthermore, more efficient strategies to solve the tasks in the tests can be applied in the second test session. Some slight but significant improvement in performance can be seen in our data; however, the changes were the same in the depression and the control group.

(3) The main reason for discrepancies in the results reported in the literature may be the duration of the testing sessions. Depressed patients usually deliberately perform the tasks if the psychiatrist in charge explains to them the reason for testing, i. e., that diagnostic clues can be drawn from the results. But any sustained effort for mental operations will most probably cause exhaustion in these patients (Whitehead 1973). Due to the short total time of testing (less than 15 min) and the short duration of individual tasks in our study the test performance of depressed patients might not be impaired by these non-cognitive factors. This may explain why no improvement could be assessed in the time course of improvement of affective symptoms. The interval between the two testing sessions was long compared with usual therapy studies, about 4.5 months. The dysfunction may be normalized slowly within months in the follow-up. But an earlier study from our group showed that deficits of depressed patients may even persist for 3 years (Reischies et al. 1990). This study shows even after a long period of remission that there was no improvement of the depressed subjects up to the level of the normal control subjects.

The results are consistent with regard to comorbidity of mild cognitive impairment and major depression. The data cannot answer the question at what time the mild cognitive impairment has started nor whether it is caused by the often found white matter lesions in depression (Brown et al. 1992, Rabins et al. 1991, Fujikawa et al. 1996, Greenwald et al. 1996, Alexopoulos et al. 1997). Also, persistent functional brain imaging abnormalities should be discussed with respect to cognitive data (Drevets et al. 1997). Theoretically a brain dysfunction, which occurred in the depression and persists, could also be discussed as causing the persistence of the cognitive disorder.

A further conclusion seems to be inevitable: the considerable change in subjectively experienced depressed mood may not be as important for performance in neuropsychological tasks as has been expected previously. This seems true at least for tests like those performed in this study. As part of the depression syndrome there is also an objective reduction of drive and spontaneous movements and – consistent with our results – also a persistence of the reduction

of spontaneous movements is reported after recovery of mood (Greden et al. 1986). Different neural substrates may be responsible for experience of mood (e. g., in relation to the emotional motor system, Holstege et al. 1996) and the integrity of cognitive functions as assessed by neuropsychological tests.

Our data did not verify a pattern of neuropsychological test performance in depression with relatively more pronounced episodic memory deficit compatible with hippocampal damage in depression. Only mild verbal and figural memory disorder without a learning deficit and a mental slowing could be demonstrated, a pattern known from subcortical dementia (Beatty 1992, Cummings 1989). Furthermore, no correlation between the cognitive deficit and the duration of the disease and the number of episodes could be found. The impaired recall of a learning list without learning- and storage deficit is consistent with a dysfunction of retrieval processes in depression. The verbal fluency task can also be regarded as a task of retrieval from semantic memory.

Further research is necessary to find neuropathological or neurochemical reasons for the cognitive deficits in about one third of the depressed inpatients. One consequence of the results is that studies of the pathophysiology and metabolic markers in depression should take into account the heterogeneity of depressed patients with respect to cognitive impairment. Accordingly, different pathophysiological mechanisms are probably to be found which might obscure findings of biological markers.

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