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ORIGINAL PAPER

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Neuropsychological performance in partly remitted unipolar depressive patients: focus on executive functioning

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Abstract *Background* Only few studies have investigated executive impairment in the euthymic phase of unipolar affective disorders, yielding diverging results. The role of impulsivity/orbitofrontal associated executive functioning in remitted depression has not yet been examined. *Methods* Partly remitted male out-patients ($n = 15$) with non-psychotic major depression (MDD) were compared with healthy males ($n = 15$) on several neuropsychological tests. Executive tasks focussed on orbitofrontal function (Go/No-Go, Iowa Gambling Task (IGT), delayed alternation task). Furthermore, the Barratt Impulsiveness Scale (BIS-11) was administered to all subjects. *Results* Executive skills of the patients were largely unimpaired. Patients exhibited significant deficits on measures of verbal memory only. Residual depressive symptoms in patients were correlated with diminished response inhibition. BIS-11 scores were not elevated in the patients. *Conclusions* Both executive impairment related to orbitofrontal function and self-reported impulsive behaviour in major depression seem to be state-dependent. In accordance with other studies, patients with remitted unipolar depression showed a persistent verbal memory loss.

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Introduction

Clinical and experimental evidence consistently shows that executive performance can be moderately impaired in depression [54]. It is less clear, however, which of these deficits persist in the euthymic phase and whether this is true for all patients with depression or just for specific subgroups [4, 40].

A majority of studies suggest continuing deficits in verbal or visual/spatial memory [23, 40, 44, 50, 53, 60] contrary to a few other findings [56, 70].

With respect to persisting executive dysfunctions some studies report executive impairment in remitted depressives [40, 50, 53, 55, 56, 60, 70] while other investigators could not detect any differences [11, 44]. Furthermore, impaired attentional performance in the euthymic phase of unipolar Depression (UD) was demonstrated in several trials [53, 70] but not supported by other authors [17, 43]. On the whole, studies examining executive and attentive performance in remitted affective disorder yield diverging results.

Several reasons might be responsible for these contradictory findings with regard to continuing deficits in executive performance. Bipolar, and unipolar as well as patients with psychotic depression are often studied together [e.g. 40, 45, 53, 67] though there is growing evidence that these depressive subtypes exhibit different cognitive deficits in the acute and euthymic phase of the illness [13, 16, 25, 28, 33, 35, 49, 56, 58, 71]. Further it has been shown that a history of suicide attempt in acute or remitted affective disorder may lead to specific executive dysfunctions [36, 38]. Even time of day must be considered since a small diurnal improvement of neuropsycho-

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Table 1 Sociodemographic and clinical characteristics of partly remitted depressed patients and control subjects

	Depressed patients	Control subjects	Statistical analysis	*p* value
N	15	15	–	–
Mean age	45.1 (11.4)	42.1 (9.8)	$t(28) = 0.77$	$p = 0.447$
Mean age at illness onset	37.0 (10.9)	–	–	–
Years passed since first episode	8.1 (9.5)	–	–	–
Number of depressive episodes	1.9 (1.5)	–	–	–
Number of hospitalisations	1.0 (0.8)	–	–	–
IQ	114.5 (12.3)	109.6 (8.0)	$t(24,2) = -1.22$	$p = 0.205$
Years of education	15.4 (2.6)	15.9 (1.7)	$t(28) = -0.59$	$p = 0.563$
Ham-D	6.3 (3.5)	1.7 (1.9)	$U = 31.0$	$p = 0.000$*
BDI	9.1 (6.1)	2.9 (3.3)	$U = 43.0$	$p = 0.003$*
BIS−11 Total	62.1 (9.7)	58.0 (9.8)	$t(28) = -1.16$	$p = 0.255$
BIS-11 Attentional	15.4 (3.0)	13.4 (2.4)	$U = 73.0$	$p = 0.106$
BIS-11 Motor	20.3 (4.6)	21.0 (4.2)	$t(28) = 0.42$	$p = 0.681$
BIS-11 Nonplanning	25.7 (4.4)	23.6 (4.4)	$t(28) = -1.33$	$p = 0.194$

Data in parentheses are standard deviations

logical performance in depressive disorder has been described [47]. Finally, duration and severity of illness, number of episodes and hospitalisations [4, 20, 40] as well as residual depressive symptoms [24, 70] possibly contribute to gain full cognitive recovery. Thus, minimising variance in clinical features e.g. by focussing on a depressive subtype could be a more successful way to demonstrate a specific cognitive profile or impairment, respectively. Therefore, in the present study only patients with unipolar depression without psychotic features and suicidal behaviour were included.

The neuropsychological deficits found in major depression are associated with changes in cerebral blood flow, metabolism and structural alterations [21, 42, 54]. While mnestic deficits have primarily been associated with hippocampal alterations (see e.g. [63]) executive dysfunctions were related to functional and structural changes in the prefrontal cortex [62]. Regarding prefrontal changes, a persisting diminished volume of the orbitofrontal cortex [14] has been reported in euthmyic depressives. Furthermore, Neumeister et al. [51] demonstrated an augmentation in orbitofrontal metabolism after tryptophan depletion in remitted depressives whereas healthy controls did not exhibit any metabolic changes. In 60% of the patients tryptophan depletion was further associated with a return of depressive symptoms. The authors suggest that orbitofrontal dysfunction might represent a trait marker for the depressive disease. Therefore, on the whole we decided to focus on neuropsychological tests associated with orbitofrontal function in order to investigate persisting executive impairment in partly remitted depressives.

Several imaging studies have demonstrated a relation between orbitofrontal activation and specific neuropsychological tests like the Iowa Gambling Task (IGT) [12], a Go/No-go task [34] and a Delayed Alternation Task [72]. Moreover, Berlin et al. [10] showed that patients suffering from orbitofrontal lesions report more impulsive behaviour as measured with the Barratt Impulsiveness Scale (BIS-11) [57]. In addition, it has been demonstrated that the neuropsychological performance in these tasks is associated with the BIS-11 [39, 65].

With regard to the acute phase of major depression Must et al. [48] found a worse decision making in unipolar depressive patients compared with healthy controls using the IGT. Furthermore, depressed patients showed a diminished response inhibition in a Go/No-Go condition [37] and were impaired in a delayed alternation task [27].

The aim of the following study was to examine the cognitive performance of partly remitted unipolar depressives with emphasis on these executive tasks associated with orbitofrontal function. We hypothesized impaired executive functioning in the patients in all tasks that were related to the orbitofrontal cortex and increased impulsivity, respectively. In line with Paelecke-Haberman et al. [55] we expected large effect sizes [18] with regard to impaired executive functioning. In order to rule out the influence of potentially persistent mnestic or attentional deficits on the expected executive impairment we assessed these cognitive domains, too.

Method

Participants

Fifteen male patients with fully or partly remitted major depression were included in the study. Diagnoses were confirmed by two independent psychiatrists. Furthermore, present and past records of the patients (as available in the archives of the hospital) were studied to validate diagnosis, number of episodes etc. Nine patients suffered from their first depressive episode [296.2, Diagnostic and statistical manual of mental disorders, DSM-IV, 3] with five patients being fully remitted (296.26). Six patients had recurrent depressive episodes (296.3) with half of the patients being fully remitted (296.36). All patients received outpatient therapy at the

Department of Psychiatry, University of Bonn. Inclusion criteria were a Hamilton Depression Rating Scale (HDRS) score <13 [23, 56] and a minimum of six months since discharge from hospital.

Exclusion criteria were a history of neurological disorder, substance abuse, bipolar disorder, psychotic symptoms, borderline personality disorder, history of suicide attempt and self-mutilating behaviour. Seven patients were treated with antidepressants; one patient further received a small dose (5 mg) of olanzapine as prophylaxis of recurrence.

Patients had been stable on these medications since discharge from hospital. The following antidepressive agents were prescribed: paroxetine (1), sertraline (1), escitalopram (2), mirtazapine (3), reboxetine (1), venlafaxine (1), bupropion (1).

15 male volunteers matched to age and IQ were recruited by means of advertisement. Exclusion criteria were a history of psychiatric or neurological disorder, previous psychotherapy and HDRS > 7. All subjects were given a multiple-choice vocabulary test ["Mehrfachwahl-Wortschatz-Intelligenztest", MWT-B, 41] to assess premorbid verbal IQ. The MWT-B consists of 37 items each comprising five words with four being fictitious and one being authentic German. The participant has to detect this "correct" German vocable. Demographic and clinical details for the two groups are presented in Table 1.

The study was approved by the local ethics committee and based on informed consent.

Study design

Due to organisational constraints, time of examination could not be held constant in the patient group. Still all subjects were invited after 12 a.m. (range 12 a.m.–19 p.m.). After attaining written informed consent all subjects were interviewed regarding inclusion/exclusion criteria. The neuropsychological tests and psychopathological ratings were administered to all subjects afterwards.

Clinical assessment

The 21-item version of the Hamilton Depression Rating Scale [HDRS-21; 29] and the Beck Depression Inventory [BDI; 7, 31] were used to assess severity of depression. The rating of the subject's depressive symptoms was conducted by a trained psychologist.

Impulsivity was rated by the Barratt Impulsivenss Scale [BIS-11; 57]. The BIS-11 subdivides impulsivity into three dimensions: Attention, Motor and Non-planning.

Neuropsychological assessment

(1) Iowa Gambling Task (IGT) [5, 6]. We administered a modified computer based version of the IGT (programmed by co-author Christian Hoppe), described in detail by Quednow et al. [59]. The IGT is employed to assess decision-making. The subject was instructed to gather as much (virtual) money as possible by drawing cards from four decks (A, B, C and D). Each deck consists of 40 cards. Two decks (A and B) yield immediate gain but also huge losses whereas the other two decks (C and D) leave a margin in the long run. 100 trials were conducted. A total score is calculated (net score) as well as a score for each consecutive block of 25 cards.

(2) Go/No-Go Task [52]. We employed a computerised version of the Go/No-Go Task (Go/No-Go version 1.2; Hiloma Software Development, Montreal, Canada) introduced by Newman and Kosson [52]. A detailed description of the task is provided by Quednow et al. [59]. Learning by trial and error the participants have to press a button for "active" stimuli and resist from pressing for "passive" stimuli. Stimuli comprise of eight two-digit numbers ranging from 03 to 99 with four being active and four being passive. Correct responses are reinforced (with virtual 5 Cent), wrong reactions are punished (5 Cent). The task consists of two conditions, a reward-punishment and a punishment-reward condition. Each condition has a different set of numbers running 80 trials. Dependent variables are omission and commission errors and gain (in Cent).

(3) Delayed Alternation Task [DAT; 26]. The Delayed Alternation Task used in the present study was a computer-based modification of the DAT introduced by Freedman and Oscar-Berman [26]. The subject is instructed (on the screen) to find a star depicted on two cards, which do not differ on the reverse side. Furthermore he is informed that by pressing the right or left shift button he can decide which card he wants to turn over. In the first trial round both cards are baited with a star. When the star is found the cards are shuffled and the next trial begins. The star is located at the opposite side with regard to the participant's first choice and changed in the same manner the following trials. 25 consecutive trials succeed the first trial. The total number of errors serves as the dependent variable. A maximum of 25 errors can occur.

(4) d2-letter cancellation test (Aufmerksamkeits-Belastungstest; [15]). This test assesses selective attention. It is a paper-and-pencil cancellation test demanding speed and accuracy of performance. The participant is asked to discriminate visual similar targets (d's with two dashes) from non-targets (d's with one, three or four dashes and *p*'s with dashes). Time to cancel out targets is 4 min and 40 s. For further details see Meyer and Blechert [46]. Concentration index (KL) is calculated as dependent variable.

(5) Verbal Learning and Memory Test ("Verbaler Lern- und Merkfähigkeitstest", VLMT) [32]. To assess verbal declarative memory function, we administered the VLMT which is a German version of the Rey Auditory Verbal Learning Test [61]. The first trial may serve as a measure of verbal working memory. Further dependent variables were learning capacity i.e. the sum of words of trials (1–5), delayed recall, loss due to delay (trial 5 minus amount of words in delayed recall) and recognition.

(6) Wechsler Memory Scale-Revised [30]. Three subtests of the Wechsler Memory Scale [30] were performed by the subjects. The figural memory and visual reproduction (VR) assess the visual memory whereas the digit span forward/backward are felt to represent the phonetic loop and verbal working memory respectively.

Data analysis

All variables were tested for normal distribution by the Shapiro-Wilk's test. Variables that failed the test with $p < 0.05$ were transformed using square-root and log transformation. If they were still not normally distributed non-parametric statistical tests were applied. The following tests were used for statistical analysis: (1) t-tests for independent samples and Mann-Whitney tests for single comparisons; (2) repeated-measures analysis of variance (ANOVA) with the four blocks of the Iowa Gambling Task (IGT) as dependent variables and group as the between-subject fixed factor to analyse the IGT blocks; (3) correlation analysis (Pearson's r, Spearman's rho) were used to assess possible relations between clinical variables and cognitive deficits. For correction of multiple comparisons the Bonferroni procedure was used. Trends were reported with $p < 0.1$. All data were analysed using SPSS 11.0 for Windows.

Expecting large effect sizes with regard to differences in executive functioning the sample size of $n = 30$ would yield a statistical power to detect these differences of > 0.80 fitting Cohen's [18] recommendations.

Results

Demographics and psychiatric assessment

As presented in Table 1 the groups did not differ regarding age, years of education and verbal IQ. The patients still were significantly more depressed than controls but did not show an elevated impulsivity.

Table 2 Neuropsychological performance of partly remitted depressed patients and control subjects

	Depressed patients	Control subjects	Statistical analysis	*p* value (two-tailed)
Executive tasks				
IGT net score	17.60 (28.51)	28.00 (19.24)	$t(28) = 1.17$	$p = 0.251$
Delayed alternation (errors)	3.80 (6.12)	3.13 (2.77)	$U = 95.0$	$p = 0.486$
Go/No-Go omission errors (Condition 1)	1.73 (1.79)	1.60 (2.95)	$U = 90.0$	$p = 0.367$
Go/No-Go commission errors (Condition 1)	13.80 (8.56)	9.00 (8.95)	$U = 70.5$	$p = 0.081$
Go/No-Go gain (Condition 1)	3.85 (0.95)	4.31 (1.03)	$t(28) = 1.25$	$p = 0.220$
Go/No-Go omission errors (Condition 2)	6.93 (7.00)	6.47 (7.88)	$U = 96.5$	$p = 0.715$
Go/No-Go commission errors (Condition 2)	9.36 (9.64)	6.00 (7.79)	$U = 70.5$	$p = 0.134$
Go/No-Go gain (Condition 2)	3.23 (1.53)	3.61 (1.52)	$U = 85.0$	$p = 0.400$
Go/No-Go omission errors (Σ Conditions)	8.50 (8.26)	8.07 (8.62)	$t(27) = -0.23$	$p = 0.819$
Go/No-Go commission errors (Σ Conditions)	22.79 (10.10)	15.00 (15.94)	$U = 60.0$	$p = 0.050$
Go/No-Go gain (Σ Conditions)	7.14 (1.73)	7.92 (2.39)	$t(27) = 1.00$	$p = 0.328$
Attention				
Digit span forward	8.00 (2.07)	8.87 (2.17)	$U = 85.0$	$p = 0.267$
d2 (KL)	150.00 (40.93)	157.00 (38.21)	$t(28) = 0.48$	$p = 0.632$
Memory				
VLMT trial 1	6.33 (1.35)	7.53 (1.96)	$t(28) = 1.96$	$p = 0.091$
VLMT trial 1–5	51.33 (10.01)	59.20 (6.91)	$t(28) = 2.51$	$p = 0.015$
VLMT trial 7 (Delayed recall)	9.93 (3.56)	13.20 (2.24)	$U = 45.5$	$p = 0.004$*
VLMT trial 5 minus 7 (Loss due to delay)	2.47 (1.92)	0.93 (1.28)	$t(28) = -2.57$	$p = 0.016$
VLMT recognition	11.80 (2.96)	13.73 (1.75)	$U = 64.0$	$p = 0.045$
Digit span backward	9.93 (2.06)	8.07 (2.12)	$t(28) = 0.61$	$p = 0.546$
Visual reproduction immediate	35.87 (5.14)	38.80 (2.48)	$U = 65.5$	$p = 0.050$
Visual reproduction delayed	30.80 (7.03)	35.33 (5.19)	$U = 66.0$	$p = 0.056$
Figural memory	7.13 (1.51)	8.00 (1.51)	$U = 72.0$	$p = 0.098$

Data in parentheses are standard deviations
*Significance after Bonferroni-correction

Fourteen patients had a Hamilton score equal or smaller than 10, one patient reached a score of 12. According to Beck [8] eight patients were symptom free (BDI < 10), five patients had minimal symptoms of depression (BDI < 16) whereas two patients still showed mild/moderate depression (BDI < 20).

Neuropsychological assessment

Due to technical problems one patient could not complete the second condition in the Go/No-Go Task. Table 2 shows the means and standard deviations of the neuropsychological parameters and statistical results.

There was no difference regarding the IGT net score between patients and healthy controls. ANOVA with repeated measures did yield a significant main effect of the factor block indicating a shift in drawing cards across blocks ($F(3,84) = 16.33$; $p = 0.000$) but not an interaction between the factor block and group ($F(3,84) = 0.27$; $p = 0.844$). Neither delayed alternation nor the Go/No-Go task revealed any significant differences between patients and healthy controls. However, there was statistical trend ($p = 0.050$) with regard to increased commission errors ($\sum$ conditions) in the Go/No-Go Task in the remitted depressive patients, whereas omission errors did not distinguish between groups ($p = 0.819$).

Attention as measured with the d2-letter cancellation test and digit span forward was unimpaired in the patients.

The patients yielded trends for mnestic deficits in each parameter of the VLMT compared to healthy controls with delayed verbal memory being significantly impaired. Furthermore there were statistical trends for a difference in visual reproduction and figural memory with patients performing worse than controls.

Associations between neuropsychological and psychiatric parameters

Impulsivity as measured with the BIS-11 did not show any association with the neuropsychological performance of the partly remitted depressive patients. However, BIS-11 total score as well as BIS-11 attention were highly correlated with the BDI score ($r = 0.67$; $p = 0.006$; $r = 0.72$; $p = 0.002$).

HDRS score was significantly associated with commission errors summed across conditions ($r = 0.72$, $p = 0.004$) and showed a trend with reduced Go/No-Go total gain ($r = -0.55$, $p = 0.044$). Furthermore, there was a trend between BDI score and verbal working memory i.e. the first trial of the VLMT ($r = -0.61$, $p = 0.016$). HDRS and BDI correlated moderately themselves ($r = 0.52$; $p = 0.046$).

Number of episodes and hospitalisations did not correlate with any measure. However, age of onset showed a significant age-corrected positive association with the sum of words of trials ($r = 0.71$; $p = 0.004$) suggesting that early age of onset might lead to more severe verbal learning deficits.

None of the neuropsychological variables associated with orbitofrontal functioning were significantly correlated with each other.

Finally, we calculated partial correlations with regard to impulsivity related parameters controlling for age and IQ since both variables might have had an influence on impulsivity [39]. Though not being significant we found two trends between BIS−11 attention and Go/No-Go commission errors ($\sum$ conditions) ($r = 0.53$; $p = 0.077$) and IGT net score and Go/No-Go commission errors (condition 1) ($r = 0.52$; $p = 0.086$).

Discussion

To our knowledge, this study is the first to examine exclusively unipolar patients without psychotic symptoms in euthymic state with the IGT, the Go/No-Go and delayed alternation task. In contrast to our hypotheses patients were unimpaired in the executive tasks associated with orbitofrontal function and did not report increased impulsive behaviour. Thus, neuropsychological deficits related to orbitofrontal function in depressives found by several authors [27, 37, 48] seem to be state dependent. In accordance with Dalgleish et al. [19] and Jollant et al. [36] the partly remitted depressives of our study showed no deficits in the IGT. The correlation between the impaired response inhibition and residual depressive symptoms indicates a state dependency, too. Neumeister et al. [51] demonstrated a return of depressive symptoms after tryptophan depletion in remitted depressive patients. Still, there was no difference with regard to orbitofrontal metabolism between patients who had a recurrence of depressive symptoms and those who did not. Therefore, depressive symptoms may not be directly linked with metabolism or neuropsychological functioning of the orbitofrontal cortex, respectively.

Furthermore, in opposite to the results of other authors [39, 64, 65] we could not find any association between impulsivity/orbitofrontal related measures. However, as suggested by Evenden [22] impulsivity has many different facets, which do not necessarily converge with each other. Finally, our sample might have been too small to yield significant associations since the magnitude of the correlations corresponded those found by Keilp et al. [39].

The remitted depressives yielded persistent verbal memory deficits with reduced delayed recall featuring most prominently. This result is in keeping with other studies reporting verbal long term memory deficits in euthymic patients with unipolar major depression [44, 50, 59]. Depressive symptoms did not reveal any correlations with the memory deficits found suggesting that the continuing verbal memory impairment is independent of the severity of residual symptoms.

Our results indicate that cerebral regions underlying mnestic performance could be chronically affected by the depressive illness. This is line with Sheline et al. [63] who demonstrated an association between impaired memory and hippocampal atrophy in patients with remitted depression. Further the strong correlation between age of illness onset and memory fits the finding of Bell-McGinty et al. [9] who reported an inverse relation between the years passed since the first episode began (when controlling for current patients' ages) and hippocampal volume. Nevertheless, changes in other cerebral regions being involved in verbal memory performance, e.g. the left dorsolateral prefrontal cortex [1] could contribute to the present findings, too. Walter et al. [69] recently reported an increased activation in the left dorsolateral prefrontal cortex in partly remitted depressive patients compared with healthy controls. Hence cerebral abnormalities associated with persisting verbal memory impairment are probably not limited to hippocampal changes in patients with remitted unipolar depression.

This study has several limitations. Only a relatively small number of solely male patients was examined. Though we expected large effect sizes with regard to executive deficits and hence a sufficient statistical power, our sample may have been too small to detect these differences in cognitive performance. Accordingly, the difference e.g. in the Go/No-Go task (commission errors) might have become clearly significant in a bigger sample of remitted patients. Since patients were only partly remitted it cannot be ruled out that the trend in executive deficits (increased commission errors) will disappear when full remission is achieved. However, other authors could not find any association between impaired response inhibition and residual depressive symptoms [53]. Future studies should clarify whether fully recovered depressives demonstrate inhibition deficits as measured with Go/No-go tasks.

Finally, psychotropic medication might have had a negative impact on cognitive performance in the patients [2, 66]. However, none of the seven medicated patients received tricyclic antidepressive agents, which have a negative impact on mnestic performance [66]. Moreover, a differentiation between medicated and non-medicated patients did not change the results. Yet, a negative mnestic influence of the different serotonergic and nor-adrenergic agents prescribed to the patients cannot be ruled out [68]. Since patients still were treated in the out-patient clinic of the Department of Psychiatry this was an inevitable methodological constraint.

Conclusions

Partly remitted depressives show largely unimpaired performance in tasks associated with orbitofrontal

functioning and increased impulsivity. A subtle inhibitory dysfunction in the Go/No-Go task was strongly associated with the residual depressive symptoms, suggesting state, rather than trait dependency. Overall, executive functioning related to the orbitofrontal cortex seems to be restored in the remitted phase of the illness. In opposite to that remitted patients with unipolar Depression demonstrate a persistent verbal memory loss that is independent of the residual depressive symptoms. An early onset of major depression might worsen these mnestic deficits.

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