Neuropsychological Predictors of the Clinical Response to Cognitive-Behavioral Therapy in Patients with Major Depression

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Abstract: Aim of the study was to identify neuropsychological predictors of the clinical response to cognitive behavioral therapy (CBT) in patients with major depression. 19 unmedicated patients underwent neuropsychological testing at baseline and subsequently were assigned randomly to CBT over 3 weeks either as monotherapy or combined with sleep deprivation (SD) therapy (two nights of total SD / week). Hierarchical regression analysis revealed that parameters of declarative verbal memory and a word fluency task predicted the clinical response (percentage improvement of Hamilton depression scores) to CBT monotherapy, whereas no such prediction was obtained in the combination group. The results suggest that certain cognitive performances have a unique predictive value for the response to CBT, which appears to be abolished by additive treatments with cognitive side effects (e.g. SD).

Keywords: depression, cognitive-behavioral therapy, neuropsychology


Schlüsselwörter: Depression, Kognitive Verhaltenstherapie, Neuropsychologie

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Introduction

Numerous studies have shown that major depressive disorder (MDD) is a disabling psychiatric condition associated with an impaired functioning in a variety of cognitive domains such as in attention, declarative memory and executive function, including cognitive inhibition, planning, divergent or problem-solving thinking (Marazziti, Consoli, Picchetti, Carlini & Faravelli, 2010). Although these dysfunctions are typically described in patient samples suffering from recurrent episodes, a recent meta-analysis found strong evidence for such a cognitive deficit pattern already in first-episode patients (Lee, Hermens, Porter & Redoblado-Hodge, 2012). Critically to the concept of pseudodementia (Kiloh, 1961), interpreting cognitive impairment in MDD solely as an epiphenomenon of depressive symptomatology, there are on the one hand negative findings regarding a correlational relationship between severity of mood symptoms and cognitive performance (McClintock et al., 2010; Trichard et al., 1995), and on the other hand several reports showing at least residual cognitive impairments after clinical recovery (Reischies & Neu, 2000; Neu et al., 2005; Reppermund et al., 2007). Together with a recent study demonstrating that memory impairments were already present in healthy subjects at high familial risk of depression (Mannie, Bornes, Bristow, Harmer & Cowen, 2009), these longitudinal data support the view that cognitive deficits – at least in specific domains – reflect a more trait-like (than state-like) characteristic, which is closely linked to the pathophysiology of MDD. Further studies underlined that the various cognitive deficits in MDD appeared differentially affected by genetic risk and were found to be specifically related to neuroendocrine, neuromedical and functional abnormalities (Mannie et al., 2009; Hinkelmann et al., 2009; Abercrombie et al., 2011; Turner, Furey, Drevets, Zarate & Nugent, 2012).

While there is growing research exploring the exact nature and causes of the cognitive deficits in major depression, their relevance for the prediction of the clinical course and functional outcome has – in comparison to the field of schizophrenia (e.g. Nuechterlein et al., 2012) – been rarely investigated and is still poorly understood. The majority of studies in this field were performed on elderly depressed patients, and demonstrated that cognitive impairment, preferentially of executive functioning and cognitive speed, predicts non-response to antidepressants (Kalayam & Alexopoulos, 1999; Bogner et al., 2007; Morimoto et al., 2012; Sheline et al., 2012), suggesting a mediating role of fronto-striatal dysfunction for a poor clinical response. Interestingly, the finding of a prognostic value of dysexecutive functioning for non-responding to antidepressant treatment and worse social and occupational outcome at follow-up holds also for young patients (Dunkin et al., 2000; Withall, Harris & Cumming, 2009), supporting the idea that a “executive dysfunction syndrome” and its potential neurobiological correlates play generally a key role for responding to antidepressant treatment and the clinical outcome. However, the empirical evidence to support this assumption is probably limited to pharmacological treatment, because no study has so far explicitly investigated the role of cognitive impairment for predicting the clinical outcome for other forms of treatments, especially for psychotherapy. This lack of empirical evidence for predicting the clinical response to psychotherapy is remarkable in two respects. First, psychotherapy, specifically cognitive behavioral therapy (CBT), is regarded as a first choice intervention for treating both younger and elderly patients with major depression, inclusive high-severity patients (Driessen, Cuypers, Holton & Dekker, 2010). A recent meta-analysis (Cuypers, Smit, Bohlmeijer, Holton & Andersson, 2010) investigating the efficacy of CBT compared with a control condition revealed a mean effect size according to Cohen’s d of 0.69, representing a medium treatment effect. Adjustment for publication bias resulted in a reduced effect size of 0.42. Given that there is also non-responding to CBT in up to half of patients (e.g. Luty et al., 2007), it is of high clinical relevance to predict which patients are likely to respond. Second, CBT explicitly aims to correct cognitive biases such as inaccurate beliefs and maladaptive information processing, which are assumed to play a causal role in the development and maintenance of depression (Beck, Rush, Shaw & Emery, 1979). Since the corresponding techniques of CBT require cognitive skills in various domains such as attention, memory and executive functioning (Deer, Copeland & Cheavens, 2011), it seems highly plausible that patients’ cognitive status affects their ability to assimilate adequately certain key components of CBT and to achieve a clinical benefit by these interventions.

From a clinical perspective, it should be noted that inpatients suffering from MDD are rarely treated with CBT alone, but in combination with other “somatic” antidepressant treatments such as antidepressants, electroconvulsive therapy (ECT) or sleep deprivation (SD) therapy. Interestingly, some of these clinically effective treatments are known to exert itself cognitive side-effects, which might interfere with CBT. For example, among the antidepressants, specifically the tricycles produce cognitive impairment by its sedative and anticholinergic properties (Stein & Strickland, 1998). At least transient cognitive impairments are frequently also observed in patients with MDD after ECT (Verwijk et al., 2012). Surprisingly, no study has so far investigated the immediate cognitive effects of sleep deprivation therapy in MDD. However, considering studies performed on healthy subjects that showed substantial negative effects on attention, memory and executive functions after already one night of SD (Killgore, 2010), such unwanted cognitive effects are – in spite of its antidepressive action – also likely in patients with MDD and might interfere with the patients’ ability to meet the cognitive demands of a concurrent CBT.

Altogether, it seems to be of clinical importance to assess the predictive power of baseline neuropsychological variables, which are known to be affected by MDD (attention, memory, executive functions), for the clinical outcome after CBT. Furthermore, as a test for naturalistic scenarios
of combination treatments, the predictive power should be compared between CBT monotherapy and a combined treatment of CBT and an additional – clinically effective but probably cognitive deteriorating therapy – i.e. sleep deprivation therapy.

We hypothesized that the neuropsychological variables, especially the test scores for executive function, are significant predictors for the short-term clinical outcome after an intensive CBT monotherapy over three weeks. Furthermore, prediction of treatment response could be complicated by additional SD therapy without having the empirical basis for directed hypotheses. The latter part of the study is therefore a pilot one.

Materials and Methods

Subjects

20 inpatients with a current Major Depressive Disorder (MDD) with either a single or a recurrent episode according to the DSM-IV criteria participated in the study. They were recruited from consecutively admitted patients for hospital treatment. In order to obtain a reliable diagnosis of a MDD and of other concomitant mental disorders, each patient was interviewed by an experienced psychiatrist, who used the German version of the Structured Clinical Interview for DSM-IV (Wittchen, Zaudig & Fydrich, 1997). Patients with a comorbid axis-I or axis-II disorder were excluded from study participation. Furthermore, suicidal tendencies before or during the study period as well as any change of diagnosis during inpatient treatment led to exclusion. Further exclusion criteria were neuropathies, disk diseases, nerve injuries at the upper extremities, endocrine disorders, dermatosis at the upper extremities, pregnancy and shift work within 3 months or transmeridian travel within 1 month prior to the study. Some of the above mentioned criteria have as rationale to only include patients with an intact nociceptive system because the patients took also part in pain related tests, the results of which had been reported elsewhere (Kundermann, Hemmeter-Spernal, Huber, Krieg & Lautenbacher, 2008). All patients were studied drug free. In case of prior medications, there was a minimum of a 6-day wash-out period, the exact duration of which was at least 3 times the half-life of the respective drug and its active metabolite. One patient withdrew from the study after one week and was excluded from statistical analyses.

Table 1 shows the major sociodemographic and clinical characteristics of the remaining 19 patients.

The protocol was approved by the ethics committee of the medical faculty of the University of Marburg, Germany; all patients gave written, informed consent.

Study design and time schedule

All patients underwent a treatment period of three weeks, in which they were basically treated with CBT. According to randomization, the patients received either the CBT alone or in combination with sleep deprivation therapy. Each patient of the SD group underwent two nights of total sleep deprivation within one week (on day 1 to day 2 and on day 4 to day 5; see Fig. 1). Accordingly, treatment nights were separated by intervals of two or three days with normal (recovery) night sleep. This sequence of SD nights was repeated during the second and third treatment week. Patients of CBT monotherapy group had regular bed times for the whole study period.

All patients underwent three days prior to treatment a comprehensive neuropsychological testing battery. The assessments of depressive symptomatology were also performed at baseline and after each treatment week.
Treatments

Each study patient received an intensive (5 sessions weekly) manualized CBT (Hautzinger, Stark & Treiber, 2000), which in its initial part mainly focused on behavioral activation (i.e. a gradual increase of frequency and subsequent positive reinforcement of depression-incompatible activities based on a detailed assessment of contingencies maintaining depressive behavior and goal setting strategies). Subsequently, a cognitive treatment module was performed, which targeted on patients’ (dysfunctional) evaluations and attributions of causality or responsibility by various cognitive techniques (e.g. differentiating between situations, thoughts and emotional reactions, teaching the patient to recognize when thinking falls into the category of a specific cognitive error, identifying and re-evaluating distorted cognitions and dysfunctional beliefs). While the behavioral and cognitive treatment modules were conducted as individualized sessions, an accompanying social skill training was performed as group therapy.

Patients of the combination therapy group underwent – in addition to CBT – sleep deprivation therapy, in which a staff member monitored the patient and ensured to staying awake from 8:00 p.m. to 7:00 a.m. by engaging in standardized activities (including conversation, watching television, going for a walk, or playing games). The subject’s behavior was recorded each hour. For the patients of the CBT monotherapy group, lights were turned off between 10:00 p.m. and 11:00 p.m. to enable sleep; they were awakened at 7:00 a.m.

Neuropsychological testing

The neuropsychological tests were selected on the basis of their relative sensitivity to cognitive deficits (i.e. problems with attention, memory and executive abilities) commonly observed in patients with major depression and other clinical conditions (Hemmeter & Kundermann, 2012). A battery of the following 6 neuropsychological tests was administered:

a) As a measure of selective attention, we chose the “d2”-letter Cancellation Test (Brickenkamp, 2002), a paper-and-pencil test, which consists of 14 lines, each of it presents 47 letters. Test items are the letter “d” and “p” marked with one to four dashes arranged singly or in pairs and upward or downward signs. This tests requires to discriminate target letters (i.e. “d” with two dashes) from nontarget letters (i.e. either the letter “d” with one, three, or four dashes, or in each case the letter “p” irrespective from the number of dashes). Each subject is given 20 seconds to cross out all targets in one line. The main parameter considering accuracy and speed performance is the difference of the number of all crossed out targets minus errors (i.e. omissions and crossed out nontargets).

b) For measuring divided attention, the Divided Attention task of the Test of Attentional Performance (TAP) by Zimmermann & Fimm (1993) was used, which requires to respond as quickly as possible to visuo-spatial and auditory stimuli. In the visual task, participants see a display with 16 points (four in each row and column). Some of them present crosses, which change their positions in the 4 x 4 matrix. Participants have to press the reaction button when four crosses form a small square. In the auditory task, a mostly alternating sequence of high and low tones is presented. The performance is expressed by the median of reaction times and the number of misses and false positives.

c) The ability to switch the focus of attention was measured by the task “Flexibility”, also a subtest of the TAP. On the right and left of the center of the screen, two stimuli (one is always a letter, the other is always a number) are simultaneously presented. Patients have to press one of
two response buttons (one for the right and one for the left hand) depending on whether a critical stimulus appears on the right or the left side, i.e. in the first trial they have to react to the letter, in the second, they have to react to the number, in the third again to the letter, and so on. The task consists of one hundred trials, in which the median of reaction times and the number of errors are the parameters of interest.

d) The information processing speed component of attention was assessed by the Zahlen-Verbindungs-Test (ZVT, Oswald & Roth, 1987), a paper-and-pencil test similar to the international more established trail-making test (TMT, part A). The ZVT consists of four matrices, in which the subject has to connect with a pencil consecutive numbers from 1 to 90 as fast as possible. The performance parameter in this task is the mean processing time for the four matrices.

e) Within the domain of executive functions, we assessed short-term signs of depressive mood states, which are not depressive symptoms and is particularly designed to assess neuropsychological testing in order to evaluate how the concurrent mood moderates the test performance. The DS is a 16 item self-rating scale to evaluate the severity of depressive symptoms and is particularly designed to assess short-term signs of depressive mood states, which are not adequately addressed by HDRS and BDI. The higher the score, the worse the patient’s condition was at the time of evaluation. This relation applied to all three scales.

The sequence of test application was always the same: AVLT, d2-Test, TAP-Divided Attention, TAP-Flexibility of Attention, word fluency by subtest 6 of LPS, ZVT and finally the delayed recognition task of the AVLT. Completion of the test battery took approximately 60 min.

**Assessment of severity of depressive symptoms**

For the assessment of the severity of the depressive symptomatology over the previous 7 days, the 21-item Hamilton Depression Rating Scale (HDRS, Hamilton 1960) and the Beck Depression Inventory (BDI, Hautzinger, Bailer, Worall & Keller, 1995) were applied at baseline and after each treatment week. The HDRS were filled out by a small group of experienced psychiatrists (J. H.-S., P. S., M. H., S. G.), who were blind to all neuropsychological assessment results. In order to achieve high interrater-reliability, they were specifically trained in the use of this instrument.

Furthermore, the Depression Scale (DS) of von Zerssen (1976) was administered immediately before starting the neuropsychological testing in order to evaluate how the concurrent mood moderates the test performance. The DS is a 16 item self-rating scale to evaluate the severity of depressive symptoms and is particularly designed to assess short-term signs of depressive mood states, which are not adequately addressed by HDRS and BDI. The higher the score, the worse the patient’s condition was at the time of evaluation. This relation applied to all three scales.

**Statistical Analysis**

Data were statically analyzed by using SPSS version 11.0 for Windows. Exploratory analyses of the data included descriptive statistics as well as tests on normal distribution and homogeneity of variance and were run to verify whether the data qualify for parametric statistics. Results are presented as mean and standard error of the mean (SEM).

At first, the Student’s t-test for dimensional data and the χ²-test for categorical data (e.g. gender, type of MDD) were conducted to compare both treatment groups (CBT monotherapy vs. CBT with additional SD) at baseline. Patients’ clinical responses to treatment were analyzed by an ANOVA with one between-subject factor “treatment” and one within-subject factor “time” evaluating longitudinal changes over three weeks, supplemented by a responder analysis using the χ²-test to compare the portion of patients with clinically meaningful improvements. Subsequently, correlation analyses were performed to determine whether there was any association between cognitive functioning at baseline and clinical improvement as expressed by the percentage decrease in the HDRS scores. In order to detect treatment specific relationships, correlation coefficients were calculated for the whole sample as well as for each treatment condition separately. Finally, stepwise hierarchical regression analyses were performed to exam-
whether and which cognitive parameters at baseline independently contribute to the variance in clinical improvement as indicated by the percentage decrease in the HDRS scores. The significance level was set at $\alpha < 0.05$.

**Results**

**Baseline characteristics of the whole sample and the two treatment groups (CBT monotherapy vs. CBT with additional SD)**

The study sample was middle-aged and relatively balanced with regard to sex (see Tab. 1). Educational level was comparable to that reported in other studies with depressed inpatients. For the majority of the patients, the diagnosis of a single episode was fulfilled. The mean severity of depression at baseline, as determined by the HDRS, BDI and DS, the latter just assessed before the neuropsychological testing, indicated a moderate to severe level of depressive symptoms. For all these sociodemographic and clinical variables, a statistical comparison between both treatment groups yielded no significant differences (see Tab. 1). Furthermore, t-test comparisons revealed that both treatment groups did not differ in their cognitive performance as assessed by the neuropsychological testing (all $p$’s $> 0.05$).

**Treatment effects of CBT monotherapy vs. CBT with additional SD on depressive symptomatology**

A marked improvement in the core symptoms of depression was observed from baseline week to the final assessment after the third week of treatment (Fig. 2).

ANOVA revealed a significant main effect for “time” in HDRS ($F(3,51) = 29.647; p < 0.001$) and BDI (Greenhouse-Geisser adjusted $F(1.806,30.7) = 8.042; p = 0.002$). As shown in Figure 2, post-hoc analyses for HDRS by using pooled data from both treatment groups showed a substantial decrease of depressive symptoms during the first week and slighter but ongoing reductions over the further course of treatment. In contrast, a significant reduction of the BDI scores was only detected after the first week whereas the differences between the following time points remained insignificant. For both measures, neither a main effect of “treatment” ($F(1,17) = 0.014; p = 0.91$ for HDRS and $F(1,17) = 0.204; p = 0.63$ for BDI, respectively) nor an interaction effect between “treatment” and “time” (HDRS: $F(3,51) = 0.429; p = 0.73$; BDI: Greenhouse-Geisser adjusted $F(1.806,30.7) = 0.775; p = 0.46$) was observed, indicating that both treatment groups did not differ in their clinical time course.

When classifying all patients ($n = 19$) according to their percentage decrease in the HDRS and BDI scores from baseline to the end of treatment into responders (improvement $\geq 50\%$) vs. non-responders ($< 50\%$), a substantial portion of patients showed a clinically meaningful response ($n = 10$ with $\geq 50\%$ HDRS improvement, $n = 9$ with $\geq 50\%$ BDI improvement). The ratio of treatment responders to non-responders was equally distributed between the two treatment conditions (ratio responders/non-responders according to HDRS: 6/4 under CBT monotherapy vs. 4/5 under CBT with SD, $\chi^2 = 0.460, df = 1, p = 0.498$; according to BDI classification: 5/5 under CBT monotherapy vs. 4/5 under CBT with SD, $\chi^2 = 0.059, df = 1, p = 0.809$).

The responder classification on the basis of the percentage reduction of the HDRS and BDI scores showed a substantial overlapping. Seven of 10 patients (70%), who were classified as responders according to their HDRS improvement, showed also a decrease of $\geq 50\%$ in the BDI. The reverse ratio was 7 of 9 (78%) ($\chi^2 = 4.337, df = 1,$)
Because of this strong overlap, we decided to conduct our further analyses exclusively on the basis of the HDRS, because this inventory is more established in studies using responder-classifications and predicting clinical outcome.

Correlation analysis between measures of cognitive functioning at baseline and clinical improvement

Correlation analyses between neuropsychological variables and improvement of depressive symptomatology after treatment revealed partly substantially und statistically significant positive relationships, indicating that a better cognitive performance was associated with a more favorable clinical course. However, as shown in Figure 3, this result pattern was consistently obvious under conditions of CBT monotherapy, but not in patients treated with CBT and additional SD.

Thus, we observed specifically for the CBT monotherapy group strong and significant associations between various measures of cognitive functioning (i.e., processing speed, word fluency performance and declarative memory functioning performance such as in trial 5, $\Sigma$ trial 1 – trial 5 and regarding the delayed recognition task) and clinical improvement, whereas those relationships could not be detected for the combination therapy group.

Hierarchical multiple regression analysis predicting clinical improvement by measures of cognitive functioning

Taking into account confounding variables and multicollinearity among the various neuropsychological measures, we conducted hierarchical multiple regression analysis to assess the unique (non-overlapping) contribution of specific cognitive measures to the prediction of clinical improvement. In a first step, age, sex and educational level were entered into the equation to control for sociodemographic variables. In a second step, type of MDD as well as baseline severity of depression were considered, i.e. HDRS, BDI and DS scores, the latter ones assessed just prior to neuropsychological testing. Subsequently, measures of attention and executive functioning were included, followed finally by the main parameters of declarative memory. The variables were entered when the probability of F was less than or equal to 0.05 and removed when it was greater than or equal to 0.10.
Results for the hierarchical regression performed to predict clinical outcome are presented in Table 2.

On the basis of the whole sample irrespective of treatment assignment, a significant predictive value was found for age, explaining 29.4% ($F = 7.089, df = 1.17, p = 0.016$) of the variance in HDRS improvement after step 1 (Model 1), but in an unexpected manner (i.e. obtaining a positive relationship between age and clinical improvement). While no substantial contribution was found after including clinical, attentional and executive measures (step 2 and 3), AVLT-delayed recognition – entered in step 4 – was the strongest predictor for clinical improvement. In summary, model 2 incorporating both variables explained 56.5% of variation in HDRS change ($F = 10.396; df = 2.16; p = 0.001$).

When conducting this approach separately for the CBT monotherapy group, this time the word fluency test of the LPS was the first extracted variable predicting significantly the HDRS response (model 1: $R^2 = 0.425; F = 5.931; df = 1.8; p = 0.041$). Once again, AVLT-delayed recognition uniquely predicted clinical response and was therefore included in model 2, explaining – together with word fluency performance – 71.3% of variance ($F = 8.696; df = 2.7; p = 0.013$). In contrast to this, applying hierarchical regression on the group treated with CBT and SD, no variable was identified to be useful to predict HDRS change.

### Discussion

The major finding of the present study was that the clinical response of middle-aged patients, who suffer from a MDD and were treated with an intensive CBT over three weeks, was – independently from other sociodemographic or clinical variables – substantially predicted by neuropsychological measures of cognitive functioning assessed prior to treatment. Delayed recognition performance and word fluency predicted significantly the clinical response to CBT but only as monotherapy and not in combination with serial SD.

For a better understanding, the therapeutic effect of CBT should be discussed first. Although the patients underwent an only short but intensive CBT program of three weeks, approximately half of the patients showed a clinically meaningful response (i.e. $\geq 50\%$ decrease of HDRS or BDI scores), which is remarkable similar to what has been observed in CBT trials of longer duration, e.g. 16 weeks in the study of Konarski et al. (2009). As already shown in a previous paper (Kundermann et al., 2008), both groups experienced a similar, gradual and significant decline of depressive symptoms indicating that sleep deprivation did not add substantially to the long-term alleviation of symptoms. Despite of this similarity in course, the predictors of alleviation were completely different in the two groups, with neuropsychological measures being only good predictors for the CBT outcome as monotherapy, whereby parameters of declarative memory were significantly predictive for the treatment response. It has to be emphasized that the predictive power by delayed recognition, in a task reflecting consolidation processes in declarative memory, was yielded after controlling for all other clinical, sociodemographic and especially neuropsychological variables. One might cautiously conclude that declarative verbal memory is a predictor for the success of a psychotherapy, which strongly depends on patients ability to memorize explicit verbal instructions for practicing skills in and between sessions as it is required in CBT. In correspondence to our data, declarative verbal memory performance, assessed prior to CBT, was shown to be predictive of the outcome in various other clinical conditions such as in schizophrenia (Penades et al., 2010), posttraumatic stress disorder (Wild & Gur, 2008), obsessive-compulsive disorder (D’Alcantare et al., 2012) or anxiety disorders following traumatic brain injury (Hsieh, Ponsford, Wong & McKay, 2012), probably indicating an overall relevance of verbal memory performance when treating patients suffering from a wide range of psychiatric disorders with CBT.

Contrary to this view of a specific role of declarative memory for benefitting from CBT, one may argue that depressive patients with largely intact memory performances simply have a favourable course in general, irrespective whether they are treated with CBT, other evidence based therapies (such as pharmacotherapy or electroconvulsive therapy) or even when they remain without any treatment. This alternative explanation cannot be com-

### Table 2

Hierarchical multiple regression analysis, performed on the whole sample and separately on both treatment groups, predicting clinical improvement from sociodemographical, clinical and neuropsychological variables

<table>
<thead>
<tr>
<th>Sample</th>
<th>Model</th>
<th>Predicting variable</th>
<th>β</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Sample</td>
<td>1</td>
<td>age [years]</td>
<td>0.542</td>
<td>2.663</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>age [years]</td>
<td>0.475</td>
<td>2.860</td>
<td>0.011</td>
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<tr>
<td></td>
<td></td>
<td>AVLT-delayed recognition: hits minus FP [N]</td>
<td>0.525</td>
<td>0.157</td>
<td>0.006</td>
</tr>
<tr>
<td>CBT Monotherapy</td>
<td>1</td>
<td>LPS – word fluency: written words [N]</td>
<td>0.652</td>
<td>2.435</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>LPS – word fluency: written words [N]</td>
<td>0.453</td>
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<td></td>
<td></td>
<td>AVLT-delayed recognition: hits minus FP [N]</td>
<td>0.572</td>
<td>2.647</td>
<td>0.033</td>
</tr>
</tbody>
</table>

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pletely ruled out with these data, because in our study patients were basically treated with CBT and other monotherapies or a waiting control group were not included, which is a limitation of the study.

The performance in a word-fluency task, indicating divergent thinking and problem solving abilities, predicted – independent from declarative memory – also the clinical response exclusively to CBT monotherapy. Unfortunately, a comparison to other studies, which highlight the predictive role of executive functions for treatment response, cannot be made because almost exclusively pharmacologically treated depressed elderly patients served as subjects in these investigations (e.g. Bogner et al., 2007; Morimoto et al., 2012; Sheline et al., 2012).

This leads to the question by which mechanism additional serial SD abolishes the predictive value of neuropsychological parameters for the clinical response to CBT. SD in MDD can produce – in spite of its short-term antidepressive properties – unwanted effects the next day such as excessive daytime sleepiness and reduced vigilance (Hemmeter, Hatzinger, Brand & Holsboer-Trachsler, 2007). Moreover, several studies performed on healthy subjects revealed that already one night of sleep deprivation impairs many cognitive domains such as executive functions and memory (for a review, see Killgore, 2010). According to these observations, it appears plausible to assume that these side effects interfere with the patients’ ability to follow the cognitive requirements of CBT. Considering in addition the substantial interindividual variance in the clinical response to SD in MDD (Giedke & Schwarzer, 2002) and also the differential neurocognitive vulnerability to SD (Chua, Venkatraman, Dingès & Chee, 2006), the neuropsychological baseline examination of patients subsequently treated with CBT and serial SD did not longer sufficiently reflect the cognitive status in the further course of treatment. In other words, the series of SD nights varied repeatedly the cognitive status and might thereby undermine its predictive power.

In contrast to the neuropsychological measures at baseline, sociodemographical or clinical variables were of no predictive value, with the exception of age when considering the pooled sample. Surprisingly, older age was accompanied by a better response to CBT, which contradicts studies reporting an opposite relationship (e.g. Fournier et al., 2009). However, a direct comparison to these studies is not possible because we did not include patients with “late life depression”. Clinical variables such as depression severity or subtype (single vs. recurrent episode) failed to predict clinical responding to CBT. This might simply be due to the small sample size and therefore the lack of statistical power to identify additional significant predictors, which is a further limitation of the study.

In summary, this is the first study demonstrating that the clinical outcome of middle aged patients suffering from MDD treated with CBT was substantially predictable by neuropsychological variables assessed prior to treatment, namely verbal declarative memory and verbal fluency.

Conclusions

The possible clinical implications of the present study findings are as follows: Neuropsychological assessment is an easily applicable diagnostic tool for depressive patients, which can provide predictive information about the clinical outcome. Independently of other clinical characteristics such as severity of depression, patients with good cognitive functioning appear to be successfully treatable with CBT. Our data further suggest, that combining CBT with other antidepressive treatments, known for their cognitive side effects like SD and probably also with ECT or tricyclics, diminishes the predictive power of neuropsychological variables for a successful treatment with CBT. Thus, neuropsychological assessment may be useful for treatment planning including to adjust CBT for severe cognitively impaired patients.

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