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Cognitive deficits in the euthymic phase of unipolar depression

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ABSTRACT

Although neuropsychological deficits have been reported in patients with major depressive disorder (MDD) during an acute episode, relatively little is known about the persistence of these deficits in remission. This study investigated the performance of attention, executive function and verbal memory during remission from unipolar depressive episodes. We tested the hypothesis that outpatients do not differ in cognitive variables from controls. We did this using a well-defined outpatient sample, consisting of medicated and unmedicated patients, with a history of MDD. Ninety-seven subjects with MDD in remission ranging from young to old were compared with 97 healthy control subjects. Both samples were balanced for age, gender, and education levels. The Auditory Verbal Learning Test (AVLT) and the Trail Making Test (TMT) were used. Patients with remitted MDD, in comparison with controls, were impaired on tasks of attention, executive function and verbal memory. The individual level of depressive symptoms was not related to the cognitive performance. Small- to medium-sized significant correlations exist between cognitive test variables (as represented by Trail Making B and AVLT delayed recall) and level of depressive symptomatology (as measured by MADRS or BDI-II) in the total sample, indicating that higher levels of depressive symptomatology are associated with lower cognitive function. These findings suggest deficits in attention and delayed verbal recall can serve as an indicator for MDD in outpatients.

1. Introduction

Major depression is a chronic and disabling disorder with high rates of recurrence. Depressive disorders are highly prevalent worldwide (Ayuso-Mateos et al., 2001); in Europe about 8.56% of the population suffers from major depression. Achieving complete remission should be the standard of care in optimal pharmacotherapy (Thase, 1999). However, there are different definitions of remission — according to a consensus conference in 1988, remission was defined as a relatively brief period during which the individual is asymptomatic. It is strongly recommended (Hamilton and Abramson, 1983) that cognition during the period of symptomatic remission be assessed not only when the subjects are discharged from the hospital but also after subjects have returned to their natural environments.

Cognitive impairment associated with major depressive disorder may be a key factor affecting the subject's ability to function occupationally. Depressive patients in remission have been found to lose much occupational productivity. The average number of productive hours lost was considerably higher for patients with major depressive disorder (MDD), followed by patients in partial remission of major depression and dysthymia (Stewart at al., 2003). This evidence suggests that functioning may be impaired long before and long after the major depression episode (Hirschfeld, 1998; Ormel et al., 2004). Accumulated evidence suggests that neuropsychological deficits represent a key symptom of depression (Basso and Bornstein, 1999).

An extensive body of research demonstrates that cognitive deficits that accompany mood disorders during hospitalization are reversible following successful antidepressant treatment (Neu et al., 2005; Deuschle et al., 2004). On the other hand, patients with a history of an affective disorder have been found to have residual deficits that persist even when they are considered to be fully recovered (Chamberlain and Sahakian, 2004; Reppermund et al., 2007). The extent to which dysfunction persists after remission and the factors contributing to this persistence remain uncertain (Neu et al., 2005). Some authors report improvement of cognitive performance after remission from depression, while others do not (Reischies and Neu, 2000; Neu et al., 2005; Williams et al., 2000). The question whether cognitive deficits in depression are reversible with the remission of depression is crucial for some neuroscientific models of depression. These models include hippocampal damage (Neumeister et al., 2004; Neumeister et al., 2005) or subcortical and basal ganglia lesions (Reischies and Neu, 2000). Moreover these findings may help to design a cognitive rehabilitation program specifically for this patient group.

In MDD patients, a consistent and specific profile of neuropsychological abnormalities has not been established. It remains unclear whether cognitive disturbances persist beyond the symptomatic

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phase of MDD. Only a small number of studies have compared the performance of subjects who have recovered from depression with that of similar controls (Austin et al., 2001), especially in outpatients who function relatively well in their environments. For example, Weiland-Fiedler et al. (2004) studied middle-aged, unmedicated, discharged patients with unipolar MDD in comparison with control subjects. The results suggest ongoing neurocognitive deficits during the remission of the illness. These deficits were prominent in tests of sustained attention, and more subtle deficits were found in the mnemonic and strategic aspects of working memory. Such deficits also impaired psychomotor functioning. Paradiso et al. (1997) found cognitive deficits in hospitalized patients during the euthymic phase of chronic unipolar depression in visual-motor sequencing, executive function and memory. Another study found that patients with MDD performed more poorly in tests of attention and executive functions than the control subjects (Paelecke-Habermann et al., 2005). Kessing (1998) found cognitive impairment to be associated with the number of affective episodes experienced. On the other hand, Biringer et al. (2005) found that recovery from major unipolar depression was accompanied by many aspects of executive function returning to normal levels. According to these authors, neuropsychological deficits are reversible in recurrent unipolar depression. They found an improvement in executive functions in young depressive patients in remission (both medicated and non-medicated) in accordance with the improvement of depressive symptoms. During remission, depressive symptoms were 0.24 S.D. below levels in control subjects. These authors use their results as an argument for the model in which depression-related changes in executive functions are reversible upon recovery.

Most studies conducted during the hospitalization of younger patients found early improvements of cognitive functioning concurrent with decreases in symptoms during pharmacological treatment (Mandelli et al., 2006). On the contrary, older patients with cognitive deficits during hospitalization had a high probability of still being impaired 1 year (Bhalla et al., 2006). Some authors found that about one third of depressive patients score at an impaired level (Reischies and Neu, 2000). All together, most studies support the hypothesis that cognitive deficits exist in patients in unipolar depression during periods of remission. Kessing (1998), who summarizes older studies of cognitive deficits in unipolar depression or mixed unipolar and bipolar patients, describes 11 other studies that mention contradictory reports.

Previous studies have some methodological limitations, e.g. relatively small subject sample sizes (Weiland-Fiedler et al., 2004; Biringer et al., 2005; Marcos et al., 2005; Neu et al., 2005; Paelecke-Habermann et al., 2005); they analyzed patients during hospitalization and not while patients were residing in their natural environments (Reischies and Neu, 2000) or they combined unipolar and bipolar samples (Mandelli et al., 2006). This last limitation is crucial because patients with unipolar and bipolar disease should not be studied as having a unitary disorder (Paradiso et al., 1997).

The present study investigated performance of attention, executive function and memory during remission from a unipolar depressive episode in a well-defined outpatient sample functioning in their natural environment. Specifically, we tested a hypothesis that outpatients do not differ in cognitive variables from matched controls.

2. Methods

2.1. Sample

The study was conducted with 97 unipolar depressive outpatients (46 men and 51 women; Tables 1 and 2) from the Clinic of Prague Psychiatric Center and Psychiatric Clinic of Brno-Bohunice, Czech Republic. The mean age of the participants was 46.3 years (S.D. = 12.1; range 22–72). Among the total sample, 47 participants had a history of only outpatient treatment, 50 were hospitalized one or more times (maximum 5 hospitalizations). All of the patients met the criteria for former major depressive disorder according to ICD-10. The diagnosis was performed by the attending physician. All of the patients were in a state of remission at the time of testing. Remission was defined as a period of at least 2 months during which the subject functioned well (subjectively according to the patient and objectively according to his/her psychiatrist) and the MADRS (Montgomery-Åsberg Depression Rating Scale) score was below 12. On the day of study, all patients were given the MADRS. The mean MADRS score was 4.4 (S.D. = 3.0). Guidelines defining remission state that the score should be between 0 and 12. For all patients, information about their previous course of illness was carefully extracted from their individual case notes.

In addition, 97 control subjects matched for age, education and gender were tested. Controls were recruited from the general population through advertisements asking for the aid of unpaid volunteers. The control subjects had no known personal or family history of psychiatric disorders in first degree-relatives. The two groups differed in their scores on the BDI-II (Beck Depression Scale; two-tailed t-test, $t = 0.14$; df = 186; $P < 0.001$).

Patients and controls were screened for psychiatric, neurological and substance abuse problems. Patients were tested with the Information subtest from the Wechsler Adult Intelligence Scale-Revised, and individuals with scores corresponding to IQ < 70 were excluded. Subjects with dementia, substance abuse/dependence, neurological disorder or clinical/laboratory indications of the presence of a severe organic disease, actual or prior bipolar I or II disorder, and individuals with MADRS scores > 12 were not included in the sample. On the basis of these criteria criteria, 25 participants were not included in the study.

The depressed outpatients and the controls were all native Czech speakers due to the nature of the verbal tests. They all were Caucasians. Written consent was obtained from all participants after the design and the purpose of the study were explained. The study was approved by an Independent Ethics Committee.

2.2. Methods

The tests were selected using two criteria. First, the total testing time should be short; therefore we chose tests of short duration, which are reliably used in clinical neuropsychology. Second, the major neuropsychological domains, which were expected to demonstrate performance deficits in depression, should be assessed (Marvel and Paradiso, 2004).

All subjects were given a succession of short neuropsychological tests. Symptom scales were administered simultaneously with the neuropsychological evaluation. All the methods used in this research were previously validated for local Czech conditions. Each patient was tested individually during one session and the test succession was administered in the same order and form to all patients. Neuropsychological testing was performed within the Clinic of Prague Psychiatric Center and the Psychiatric Clinic Brno–Bohunice. All patients were tested by one of two trained administrators. The assessment took about 1 h. The test administrators were not blind to the subjects' status as a patient or control group member. Norms for obtaining z-scores were derived from a meta-analysis of studies that had previously used these tests (Mitrushina et al., 2005).

2.2.1. Memory — Auditory Verbal Learning test

The Auditory Verbal Learning test is a 15-word learning task which was repeatedly (5 times) read to the subjects. The sums of all the correctly recalled words from first five trials as well as the sum of words recalled in the delayed recall trials (after 30 min) were used as memory variables. The test proved to be valid in other studies on depression (Brandt et al., 1992). A Czech version of the test was used (Preiss, 1999).

Table 1
Family and occupational status in the outpatient group.

	N
Family status	
Single	17
Married	58
Divorced	18
Widow/er	4
Occupation	
Partially disabled	1
Partially disabled + employed	1
Unemployed	2
Maternity leave	2
Household	3
Student	4
Fully disabled	4
Old age pension	13
Entrepreneur	17
Employee	50
Medication	
TCA	20
SSRI	48
Mirtazepine	11
Other antidepressants	6