

Automated Neuropsychological Test Battery in depression – preliminary data

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Aims: Studies have demonstrated neuropsychological deficits across a variety of cognitive domains in patients with major depressive disorder (MDD) during acute episode. However, limited data are available concerning whether these abnormalities persist in the remission phase. **Methods:** In the present study CANTAB (Cambridge Automated Neuropsychological Test Battery) was used to evaluate the cognitive impairment associated with depression during acute episode and in remission. 25 patients with MDD during an acute episode and 11 patients also during remission were tested with CANTAB. **Results:** During the acute episode, *Delayed matching to sample*, *Paired associate learning*, *Spatial recognition memory*, *Rapid visual processing* and *Visuospatial planning* were impaired. In remission the improvement of visual learning ability, spatial recognition memory, psychomotor speed, and executive function was observed. **Conclusions:** The results suggest that MDD is associated with neurocognitive dysfunctions in different domains, the most prominent deficit was found in the *Paired associate learning* test, which requires both the elaboration of “frontal strategies” and the “mnemonic processes”. Cognitive impairment was found to improve partly in remission, suggesting that an individual’s current mood interacts with the ability to perform a cognitive task. Besides these state markers, trait deficits are important because cognitive impairments which do not improve in remission might serve as endophenotypes of depression.

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Neuropsychological deficits are key components of affective disorders and have been examined by different neuropsychological tests. There are several reports showing a number of deficits during the depressed state, however, less dealt with cognitive impairment during remission (Austin et al., 1999). It is largely unclear whether the neuropsychological deficits are state or trait markers of the disorder. Studies examining the way in which cognitive impairment is associated with depression have produced inconsistent findings, which may have been attributed to different severity and age of onset of depression across studies. Inconsistent findings have also been reported in relation to the specific association of depression severity with cognitive performance (McDermott & Ebmeier, 2009). Besides severity and age, many other factors may contribute to the inconsistent findings, such as hospitalisation, subtype of depression, or the effect of psychotropic medication (Grant et al., 2001; Porter et al., 2003).

Neuropsychological findings indicate widely distributed deficits in cognitive domains subserved by temporal, parietal, and frontostriatal systems in bipolar patients during mixed/manic states of illness (Weiland-Fiedler et al., 2004). In that study significant deficits in bipolar and non-bipolar depressed patients were restricted to episodic memory, suggesting a more selective dysfunction in medial temporal lobe function during episodes of depression. These findings highlight the different cognitive profiles of mania and depression. On the other hand, in unipolar depression, neuropsychological deficits previously been reported in the domains of psychomotor speed, memory, sustained attention, and executive functioning, including working memory and complex problem solving. Deficits in sustained attention as a vulnerability marker for major depressive disorder were also suggested (Weiland-Fiedler et al., 2004).

Generally a modest correlation has been reported between symptom severity and neuropsychological

deficits in depressed patients including studies showing improvement in function after treatment (Goldberg et al, 1993). However, there is a growing consensus that some neuropsychological deficits in depressed patients may persist after clinical symptom remission (Trichard et al, 1995; Sweeney, 2000). Although marked neuropsychological deficits have been reported in elderly patients and in midlife patients with severe depression, medically healthy younger ambulatory adults with depression demonstrated a notable absence of widespread cognitive impairment (Grant et al., 2001).

To understand the influence of late life depression (LLD) on cognition, it is important to determine whether deficits in a number of cognitive domains are relatively independent, or mediated by depression-related deficits in a basic domain such as processing speed. Slowed processing speed appears to be the most core cognitive deficit in LLD closely followed by executive functions deficits (Lyness et al, 1994). Cognitive impairment in LLD has also been shown to be greater in late onset depression (Sheline et al., 2006). Other studies have found no difference after correction for chronological age (Brodsky et al., 2001). The aim of the present study was to compare cognitive dysfunctions in the acute phase of major depressive disorder (MDD) and also during the remission phase in the same patients using a computerized test battery which may provide more reliable results than classical neurocognitive tests. Middle aged patients were examined to exclude bias due to age-related changes in the brain, and young aged patients were excluded because of the uncertain characteristics of cognitive impairment of young age depression.

METHODS

Patient population

The patient group consisted of 25 subjects (11 men, 14 women) with the diagnosis of major depressive disorder (MDD) according to DSM-IV criteria. Patients with bipolar depression were excluded. The mean age (\pm SD) of the subjects was 57 ± 8 years (range: 39-64) (Table 1). The diagnosis was based on the history of the patients and on detailed physical, neurological and psychiatric examinations. All patients with other first axis psychiatric disorders, other neurological, general medical disorders, or any morphological changes in the brain as assessed by CT were excluded. The diagnosis was also confirmed by the Hamilton Depression Scale (HDRS) (Table 1). Dementia was excluded

by the Mini Mental State Examination (MMSE). The examinations were performed before the initiation of the antidepressant treatment.

Of the described patient group, 11 patients meeting the criteria for remission were reassessed after six months (2 men, 9 women) in the remission phase of MDD. The mean age (\pm SD) of these subjects was 55 ± 6 years (range: 42-60) (Table 1). Patients were receiving the following medications during follow-up: SSRI – 7 patients, venlafaxin – 2 patients, mirtazapine – 1 patient, and one patient was medication free. The remission of major depression was confirmed by the Hamilton Depression Scale (HDRS, Table 1).

The subjects were informed about the aim of the study and gave their consent to participation. The study was carried out according to the Helsinki Declaration.

Study design and assessment

Subjects were asked to perform a series of 13 computerized neuropsychological tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge, United Kingdom). CANTAB has been used and proved to be a useful tool to assess cognitive functions in diverse neurological and psychiatric disorders, such as dementia, schizophrenia, depression, Parkinson's Disease (Égerházi et al., 2007; De Jager et al., 2005; Bartók et al., 2005; Ferencz et al., 2005; Weiland-Fiedler et al., 2004; Foltynie et al., 2003). Patients were seated at a comfortable height, approximately 0.5 m from the monitor, and were instructed to carry out the tasks by touching the screen. After an initial explanation and completing a simple "motor screening task" successfully (touching the centre point of flashing crosses on the screen), subjects were given the following tests in the following order (the technical description of the tests can be found on the Cambridge Cognition's website: <http://www.cantab.com>): *Big Little Circle* (BLC): a two-stimuli visual discrimination and category achievement test. *Spatial working memory* (SWM): this task assesses the subject's ability to retain spatial information and manipulate remembered items in working memory. *Reaction time* (RTI): The task is designed to measure the subject's speed of response to a visual target where the stimulus is either predictable (simple reaction time) or unpredictable (choice reaction time). *Spatial span* (SSP): A computerised version of the Corsi blocks, a test of span for spatial items similar to 'digit span' tests for verbal items. *Pattern recognition memory* (PRM):

Table 1 Mean characteristics of the patient groups

Patient group	Mean age±SD	MMSE score (mean±SD)	HDRS (mean±SD)
MDD (n=25)	57±8	28±0.2	23±5.4
MDD in remission (n=11)	55±6	29±1.6	8±3.6

a test of visual recognition memory in a 2-choice forced discrimination paradigm. *Spatial recognition memory* (SRM): this task tests visual spatial memory in a 2-choice forced discrimination paradigm. *Paired associate learning* (PAL): assessment of simple visual pattern and visuospatial associative learning, which contains aspects of both a delayed response procedure and a conditional learning task. *Intra/Extradimensional shift task* (IED): a test of rule acquisition and reversal, featuring visual discrimination and attentional set shifting and analogous to a category change in the Wisconsin Card Sorting Test. *Match to sample visual search* (MTS): a two-stimuli visual discrimination and category achievement test. *Delayed matching to sample* (DMS): this task tests visual memory in a 4-choice delayed recognition memory paradigm. *Stockings of Cambridge* (SOC): the task is analogous to the 'Tower of London' test and assesses the subject's ability to engage in spatial problem solving. This test makes substantial demands on executive function. *Rapid Visual Information Processing* (RVP): a visual continuous performance task, using digits rather than letters. Results were compared to the internal normative database of CANTAB, involving 3.000 healthy volunteers, and were matched for age-groups and gender. CANTAB tests were previously validated among Hungarian healthy volunteers showing no statistically significant differences in the cognitive performance compared to the internal normative database (Bartók et al., 2001).

Data analysis

Since no control group was used in the study, the participants' z-scores of all CANTAB subtest results were calculated from median scores on the basis of the normative database of healthy volunteers contained within CANTAB. Since normal distribution could not be assumed in all tests, the index scores of the patients and those of the normative database were compared using an one-tailed non-parametric t-test. Statistical

calculations were carried out using the GraphPad Prism 5.00 for Windows software (GraphPad Software, San Diego, CA, USA, <http://www.graphpad.com>) and $p < 0.05$ was considered as significant.

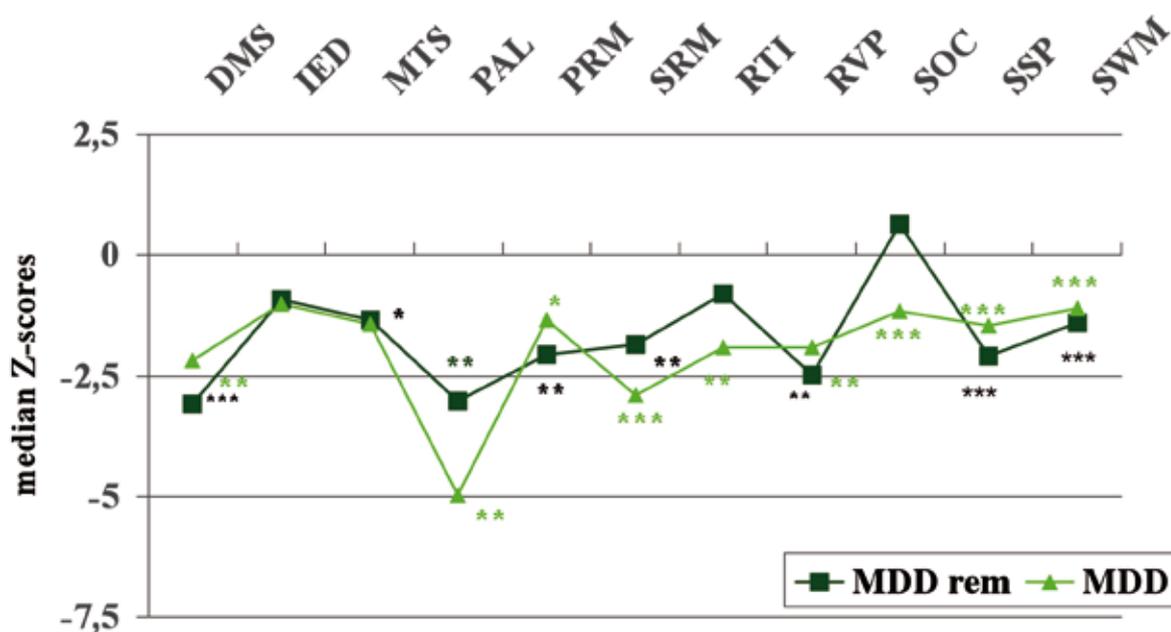
RESULTS

The cognitive performance of the MDD group was significantly lower than that of the healthy individuals, however, many of these measures improved in remission (*MDD rem*) as shown in Figure 1. The results of the individual tests for the two groups are given in Table 2. In the MDD group there was a statistically significant cognitive dysfunction in all tests except IED and MTS. In the *MDD rem* group we also observed statistically significant dysfunctions except in the tests IED, RTI, and SOC. However, there was a statistically significant improvement in the PAL, SRM, RTI, and SOC tests in the *MDD rem* group compared to the MDD group.

DISCUSSION

The results of the present study show that several cognitive domains are impaired in patients with MDD. The cognitive performance of patients was decreased on all CANTAB tests compared to normal controls and all were statistically significant except IED and MTS. The visual memory was the most impaired neuropsychological domain including PAL, SRM, and DMS tests. A successful performance in the PAL test requires both the elaboration of "frontal strategies" and the "mnemonic processes" of the medial temporal lobe (Jakala et al., 1999). The PAL task involves learning an association between visual stimuli and distinct spatial locations on a trial-by-trial basis, which has been demonstrated to decline with age in factor-analytic studies involving large samples (Rabbit & Lowe, 2000; Robbins et al., 1994). Elderly subjects with major depression perform poorly on the tests of memory, as do subjects with Alzheimer's disease (AD)

Figure 1 The pattern of median z-scores of the CANTAB tests and their difference from the control scores among subjects with MDD (n=25) and MDD in remission (n=11). Significance: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ compared to healthy individuals



(Lichtenberg et al., 1995). In our previous study, PAL test was also significantly impaired among subjects with mild cognitive impairment (MCI) which may suggest that MCI patients may already be in the early stages of the AD (Égerhazi et al., 2007). Furthermore, several studies, including functional brain imaging experiments, have shown a dysfunction of the medial temporal lobe also in the early phase of dementias and schizophrenia (Antonova et al., 2004; Twamley et al., 2006; Bartók et al., 2005). According to these results, the PAL test is an early and very sensitive marker in the cognitive assessment of different psychiatric disorders, although the specificity of such tests is particularly critical for being able to differentiate MDD, MCI or AD individuals.

Using the CANTAB neurocognitive battery Sweeney and coworkers stated that significant deficits in bipolar and nonbipolar depressed patients were restricted to episodic memory, suggesting a more selective dysfunction in mesial temporal lobe function during episodes of depression. However, robust patterns of deficits in multiple domains of function were reported in elderly depressed patients, and few cognitive deficits in younger adult patients with nonbipolar depression (Sweeney et al., 2000).

In the present study a significantly decreased performance on the SOC test was also observed suggesting the impairment of the executive functions of the patients. Gruber and coworkers compared the neuropsychological functions in patients with three different types of affective disorders – bipolar manic, bipolar depressed and unipolar depressed – in remission and they found some of the most obvious variance seems to be present in executive function (Gruber et al., 2007). Manic bipolar patients showed the worst performance, while depressed bipolar patients had a slightly better performance than depressed unipolar patients. Manic bipolar patients displayed slower reaction times which may refer to a variation in cognitive processing time rather than to slow motor speed which belongs to the diagnostic criteria for MDD according to DSM-IV (Gruber et al., 2007). In the present study psychomotor speed and sustained attention were also impaired significantly in patients with MDD (RTI, RVP).

The cognitive profile in unipolar depression demonstrates the impairment in cognition across a range of tests, subserved by neural networks, including the frontal and temporal lobes (e.g. Stockings of Cambridge (SOC) test). Research has increasingly focused

Table 2 The median z-scores of the CANTAB tests in the major depression (MDD) group (n=25) and in the remission phase (MDD rem) (n=11) compared to healthy individuals

CANTAB tests	MDD (n=25)		MDD rem (n=11)	
	Median z-scores	Significance (p)	Median z-scores	Significance (p)
Delayed matching to sample (DMS)	-2.198	<0.01	-3.095	<0.001
Intra/Extradimensional shift (IED)	-1.017	n.s.	-0.916	n.s.
Matching-to-sample (MTS)	-1.421	n.s.	-1.346	<0.05
Paired associate learning (PAL)	-4.98	<0.001	-3.024	<0.01
Pattern recognition memory (PRM)	-1.354	<0.05	-2.071	<0.01
Spatial recognition memory (SRM)	-2.892	<0.001	-1.841	<0.01
Reaction time (RTI)	-1.922	<0.01	-0.796	n.s.
Rapid visual processing (RVP)	-1.922	<0.01	-2.498	<0.01
Stocking of Cambridge (SOC)	-1.171	<0.001	0.638	n.s.
Spatial span (SSP)	-1.456	<0.001	-2.083	<0.001
Spatial working memory (SWM)	-1.094	<0.01	-1.398	<0.001

n.s.= not significant

on the idea of a dichotomy between 'hot' and 'cold' processing. 'Cold', or emotion-independent, processing is thought to utilize neural networks, including the dorsolateral prefrontal cortex (e.g. executive function tasks, SOC). 'Hot', or emotion-dependent, processing is thought to utilize neural networks including orbitofrontal, anterior cingulate, and ventromedial prefrontal cortices. Examples of hot processing are tasks that make use of affective material or produce an emotional response, such as conflict situations. Most cognitive tests will have elements of both 'hot' and 'cold' processing to different degrees, depending on the particular task (Roiser et al., 2009).

Using CANTAB in the present study, consistently with earlier research results, this cognitive profile seems to represent a mixture of temporal lobe and frontal lobe dysfunctions. In summary the affected tests included: *Delayed matching to sample* (DMS), *Paired associate learning* (PAL), *Spatial recognition memory* (SRM), *Rapid visual processing* (RVP), *Visuo-spatial planning* (SOC).

Cognitive impairment was found to improve during remission from the depressed state, suggesting that an individual's current mood interacts with his or her ability to perform a cognitive task. In the present

study we observed significantly increased z-scores in the PAL, SRM, RTI, SOC tests during remission, suggesting the improvement of visual learning ability, spatial recognition memory, psychomotor speed, and executive function. On the other hand, we were unable to find improvement in the tests of sustained attention and working-memory (RVP, SSP, SWM), as well as in a test of visual memory (DMS), similar to earlier reports (Sweeney et al., 2000; Weiland-Fiedler et al., 2004).

The degree of cognitive impairment in remission could be related to age. Some 70% of elderly depressed subjects show impairment in learning/memory tasks and response speed while depressed, but this drops to 30-40% during remission (Abas et al., 1990). It was also demonstrated that sustained attention is impaired in fully recovered unmedicated young patients, and, as in the elderly sample, the deficit is not related to residual symptoms (Weiland-Fiedler et al., 2004).

Performance of executive functions tasks (SOC) improved predominantly during remission, which test is an example for a 'cold' – emotion-independent – processing task demanding the dorsolateral prefrontal cortex, this could not be a candidate of endopheno-

types for depression. The 'hot' – emotion-dependent – processing paradigms might be a core component of the cognitive dysfunction present in depression, such as subjects' memory and attention, which are affectively biased in depressed phase.

Cognitive impairments are key components of affective disorders and, although a number of deficits exist in the depressed state, many of these disappear in remission, but some are still apparent once patients have recovered or enter a euthymic phase of illness. These trait deficits are important because they may provide clues as to the underlying neuronal and genetic basis of mood disorders, which are thought to be heritable and could be used as endophenotypes for depression. An endophenotype can be thought of as a 'hidden' phenotype that, on a functional level, lies between the overt symptoms of a disorder and the genes and pathology underlying that disorder (Gottesman & Gould, 2003). In conclusion, cognitive impairments, especially emotion-dependent, could be good candidates for endophenotypes because they fulfil many of the criteria for endophenotypes and are easy to assess without the use of invasive procedures. The limitation of the study is the small number of patients who could be retested at remission and also the practice effect in the CANTAB tests can not be fully excluded, although after six months no major effect can be expected.

Abbreviations:

AD	Alzheimer's Disease
CANTAB	Cambridge Neuropsychological Automated Test Battery
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases
MCI	Mild Cognitive Impairment
MDD	Major Depressive Disorder
PAL	Paired Associate Learning
SOC	Stockings of Cambridge

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A CANTAB alkalmazása depresszióban – előzetes adatok

Cél: A major depresszió (MD) akut epizódjában számos vizsgálat igazolja a különböző kognitív funkciók károsodását, azonban kevés adat van arról, hogy ezek az eltérések megmaradnak-e remisszióban. Jelen vizsgálatban CANTAB (Cambridge Automated Neuropsychological Test Battery) számítógépes neuropszichológiai tesztet használtunk a kognitív funkciók vizsgálatára a depresszió akut epizódjában és remisszióban. **Módszer:** 25 major depressziós beteg vett részt a vizsgálatban, közülük 11 esetben remisszióban megismételtük a neuropszichológiai vizsgálatot. **Eredmények:** Az akut epizódban a *Késleltetett mintafelismerés*, a *Párosított asszociációs tanulás*, a *Térbeli felismerő memória*, a *Gyors vizuális felismerés* és a *Térbeli vizuális tervezés* tesztek jeleztek szignifikáns eltérést. Remisszióban a vizuális tanulás képessége, a térbeli felismerés, a pszichomotoros tempó, és az egzekutív funkciók javultak. **Következtetések:** Az eredmények arra utalnak, hogy MD-ban több neurokognitív funkció is károsodik, legkiemelkedőbb eltérést a *Párosított asszociációs tanulás* teszt jelez, melynek teljesítéséhez a „frontális stratégiák” és az „emlékezeti működések” épsége is szükséges. A kognitív károsodás részlegesen javul remisszióban a depressziós epizódhoz képest, jelezve, hogy az egyén hangulata és kognitív teljesítménye között szoros kölcsönhatás van. Ezen állapotjelző markerek mellett fontosak a vonásfüggő károsodások, melyek nem javulnak remisszióban és a depresszió endofenotípusainak tekinthetők.

Kulcsszavak: kognitív funkció, unipolaris depresszió, remisszió, endofenotípus