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# Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease

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**Abstract**

Neuropsychological deficits, such as poor episodic memory, are consistent features of mild cognitive impairment and also that of early stage of dementia. The aim of the present study was to detect cognitive dysfunction among patients with Alzheimer's disease or with mild cognitive impairment (MCI), which refers to a transitional state between the cognition of normal aeging and mild dementia regarded as a high-risk condition for the development of clinically probable Alzheimer's disease (AD). Computerized tests of memory, attention and executive functions were studied in groups of AD subjects ($n=15$) and MCI subjects ($n=25$). On all measures, the performance of the AD group was significantly weaker compared to healthy individuals or to the MCI group. The performance of both the AD and MCI patients in the Paired Associate Learning test was significantly impaired, which may suggest that MCI patients are already in the early stages of the disease.


*Keywords:* Alzheimer's disease; Cognitive dysfunctions; Computerized neuropsychological test battery; Early diagnosis; Mild cognitive impairment; Paired associate learning task

## 1. Introduction

Mild cognitive impairment (MCI) is a widely cited concept in clinical research on ageing-related cognitive disorder. Generally, it refers to subclinical complaints of memory functioning in elderly people, which are considered to have a high probability of evolving towards Alzheimer's disease (AD). Cognitive impairment without dementia is so common among elderly people that it has been regarded as an inevitable feature of the ageing process. Several clinical labels have been proposed to describe this end of the normal cognitive range, such as benign senescent forgetfulness (Kral, 1962), age-associated memory impairment (Crook et al., 1986), mild cognitive decline (ICD-10, 1993), mild neurocognitive decline (DSM IV, 1994), and mild cognitive impairment (Petersen et al., 1997; De Carli, 2003). Benign senescent forgetfulness was one of the earliest terms to denote a stable impairment, commonly featuring depressive symptoms (Kral, 1962). On the other hand, age-associated memory impairment refers to subjective complaints of memory loss in elderly people, verified by a decrease of at least one standard deviation (SD) in a formal memory test in comparison with means established for young adults (Crook et al., 1986). This term was criticised by Levy and his colleagues, who found that age-associated memory impairment was a concept too restrictive in terms of the nature of the deficit and pointed out that cognitive impairment itself commonly occurs with other deficits. They proposed the term "ageing-associated cognitive decline" with a wider range of cognitive functions, such as attention, memory, learning, thinking, language and visuospatial function, and emphasized that it refers to an objective

*Abbreviations:* AD, Alzheimer's Disease; CANTAB, Cambridge Neuropsychological Automated Test Battery; CDR, Clinical Dementia Rating; CT, Computed Tomography; DSM, Diagnostic Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; MRI, Magnetic Resonance Imaging; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association—Criteria for clinical diagnosis of Alzheimer's disease; PAL, Paired Associate Learning; VD, Vascular Dementia.

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decline in cognitive functioning due to the physiological process of ageing (Levy, 1994). Within ICD-10, the criteria given for mild cognitive disorder refer to disorders of memory, learning and concentration (ICD-10, 1993). DSM-IV proposed a similar entity, "mild neurocognitive disorder", which also encompasses perceptual-motor, linguistic and central executive functions besides memory and learning difficulties (DSM-IV, 1994). Petersen and his colleagues initially used the term to refer to complaints of memory loss with normal general cognitive functioning and retained ability to carry out activities of daily living (Petersen et al., 1997). Ritchie and his colleagues examined whether this type of cognitive deficit was partly due to an underlying disease which might be differentiated from normal ageing-related physiological changes. They reviewed the conceptual basis and current clinical status of mild cognitive impairment and concluded that MCI was based on a pathological model of cognitive change, it was applicable to cognitive impairment only in elderly people, and it was not generally thought to be a direct consequence of a systemic disease, rather a risk factor for senile dementia (Ritchie and Touchon, 2000). Other authors defined MCI as a prodrome of Alzheimer's disease or a clinically heterogeneous group of patients at increased risk of dementia due to any cause. Morris (2005) suggested that MCI in many cases represents a transitional state between normal cognition and AD. The most common subset of subjects with MCI are patients with amnestic MCI, who present with a subjective memory complaint, preferably corroborated by an informant, and have an objective memory impairment compared with age-matched healthy subjects. However, they perform well in tests of general cognitive function and have generally preserved activities of daily living. Nevertheless, these subjects are likely to progress to AD. In community-based studies, individuals with MCI are about 3 times more likely to develop AD than those without cognitive impairment, and this rate is somewhat higher in persons with amnestic MCI (Petersen et al., 2001; Grundman et al., 2004, 2006). Other hypothetical presentations of MCI with slight impairments at multiple domains may progress to AD or VD, and those with single non-memory domain impairment might progress to frontotemporal dementia, Lewy body dementia, VD, primary progressive aphasia or Parkinson.s disease besides AD (Petersen et al., 2001; Dubois and Albert, 2004). Bennett et al. (2005) reported that in MCI several pathological findings similar to that of AD or cerebral infarctions were present and thus concluded that MCI might be the earliest clinical manifestation of age-related neurological diseases.

For clarity's sake, amnestic MCI is recommended to be used with its operational criteria, including (1) memory complaint, corroborated by an informant; (2) abnormal memory function; documented by delayed recall; (3) normal general cognitive function based on Clinical Dementia Rating (CDR) (Leonard, 1988) and Mini Mental State Examination (MMSE) (Folstein et al., 1975); (4) none or minimal impairments in activities of daily living (ADL); (5) not sufficiently impaired cognitively and functionally to meet NINCDS-ADRDA criteria for AD.

Several cognitive tests were applied both to MCI and AD patients to determine the specific cognitive dysfunctions in each pathology. Verbal learning and delayed recall tests proved to be useful for the detection of preclinical AD and MCI (Estevez-Gonzalez et al., 2003; Ivanoiu et al., 2005; Alladi et al., 2006), as well as several visual or other cognitive tasks, such as visual recognition, visuoconstructional performance, and semantic fluency (Malloy et al., 2003; Barbeau et al., 2004; Ribeiro et al., 2006).

Computerized neurocognitive batteries have been used in the evaluation of cognitive impairments both among AD and MCI patients. In MCI, dysfunctions were reported in memory, executive function, visual spatial skills, processing speed and cognitive flexibility (Dwolatzky et al., 2004; Gualtieri and Johnson, 2005).

The aim of our study was to compare cognitive dysfunctions in AD and MCI by a mean of a computerized test battery which may provide more objective results in the individual test than the classical neurocognitive tests. Furthermore, the computerized battery is language independent and also, as a visual test, it can be a useful tool to measure cognitive functions in patients with mild aphasia. The hypothesis was that the performance deficits of AD and MCI patients on the Cambridge Neuropsychological Automated Test Battery (CANTAB) might be similar, as MCI patients may already be in early stages of Alzheimer's disease. In early AD, novel therapeutic interventions are aimed at slowing the progression of the impairments and at delaying the onset of disability; thus, there is an increased need for diagnostic markers which may predict AD reliably.

## 2. Methods

### *2.1. Patient population*

Two patients groups were entered into the study: dementia patients and non-demented patients with amnestic MCI. A detailed clinical examination was performed on all patients including cranial computed tomography (CT) or magnetic resonance imaging (MRI). The first patient group consisted of 15 demented patients (7 men, 8 women) with the diagnosis of probable dementia of Alzheimer type (AD) according to criteria of NINCDS-ADRDA and DSM-IV. The mean age (±SD) of the subjects was 58±6 years (range: 42–83) (Table 1). The diagnosis was based on the history of the patients and on detailed physical, neurological and psychiatric examinations. All demented patients had morphological changes in the brain characteristic of AD, such as cerebral atrophy, especially in the temporo-mesial region. The diagnosis was also confirmed by the Ischemic Score of Hachinski (all patients with scores ≤4). Severity of dementia was assessed by MMSE and the average MMSE score (±SD) of the demented group was 21±1.2.

The second group consisted of 25 patients with MCI (12 men, 13 women) without any neurological symptoms or other

Table 1
Mean characteristics of the patient groups

| Patient groups | Mean age±S.D. | MMSE score mean±S.D. | CDR mean±S.D. |
|---|---|---|---|
| AD ($n$=15) | 58±6 | 21±1.2 | 2.1±1.3 |
| MCI ($n$=25) | 55±6 | 28±0.6 | 0.5 |



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physical disorders. The mean age (±SD) of the subjects was 55±6 years (range: 46–86) (Table 1). No significant differences were found between the groups in age, gender and education level. The patients had "amnestic MCI" as described above according to the criteria of Petersen, and CDR was 0.5 for all of them (Leonard, 1988). Psychiatric examination revealed mild short-term memory loss, but the symptoms were insufficient for the diagnosis of dementia according to the criteria of the DSM-IV. Mini Mental State Examination (MMSE) scores in all cases were higher than 26. CT/MRI results were normal. Patients were not receiving any medication. They were informed about the aim of the study and gave their consent to participation. The study was carried out according to the Helsinki Declaration.

### 2.2. 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 (De Jager et al., 2005; Bartók et al., 2005; Weiland-Fiedler et al., 2004; Foltynie et al., 2003).

Subjects 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 to 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 computerized version of the Corsi blocks, a test of span for spatial items similar to 'digit span' tests for verbal items. *Pattern recognition memory* (PRM): 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): It is 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).

### 2.3. Data analysis

Since no control group was available, the participants' *Z*-scores of all CANTAB subtest results were calculated from median scores on the basis of the normative database of 3,000 healthy volunteers. The index scores of the patients and those of the normative database were compared using a one-tailed non-parametric *t*-test. Statistical calculations were carried out using the GraphPad Prism 4.00 for Windows software (GraphPad Software, San Diego, CA, USA, http://www.graphpad.com) and $P<0.05$ was considered as significant.

## 3. Results

On all measures, the AD group performed significantly poorer than the healthy individuals or the MCI group, as shown in Fig. 1. The results of the individual tests for the two groups are given in Table 2.

## 4. Discussion

The present results show that several cognitive domains are already impaired in patients with MCI, and in AD patients several other cognitive domains show impairment and the severity of the cognitive dysfunctions is more pronounced.

Visual Paired Associate Learning (PAL test) was significantly ($P<0.05$) impaired among subjects with AD and MCI. 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). MCI patients performed poorly on this test, as did AD patients, which may suggest that they may already be in the early stages of the disease. Several studies, including functional brain imaging experiments, have shown a dysfunction of the medial temporal lobe in the early phase of dementia and schizophrenia (Antonova et al., 2004; Twamley et al., 2006). Furthermore, elderly subjects with major depression also perform poorly on tests of memory, as do AD subjects (Lichtenberg et al., 1995); thus, the *specificity* of such tests is particularly crucial for being able to differentiate AD individuals. Refinement of the *sensitivity* of neuropsychological tests would allow possible disease-modifying treatments to be employed at the earliest stages of



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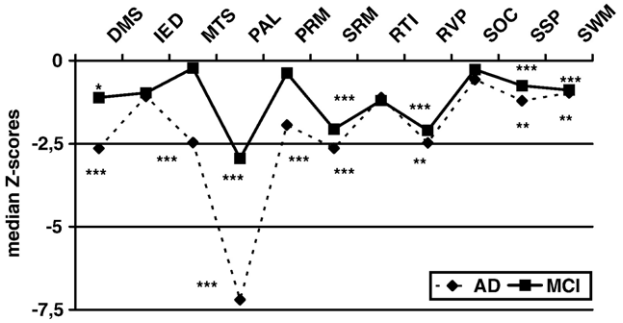


Fig. 1. The pattern of median *Z*-scores of the CANTAB test and their difference from the control scores among subjects with AD ($n=15$) and with MCI ($n=25$). Significance: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared to healthy individuals.

neuronal loss (Blesch et al., 1998). 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 (Robbins et al., 1994; Rabbitt and Lowe, 2000). Sahakian and co-workers further demonstrated impaired performance in groups diagnosed with probable AD (Sahakian et al., 1990; Sahgal et al., 1991). Gould and co-workers studied whether the same cognitive processes are in operation when a task is performed at an 80% success level, compared to a 20% success level. They found a differential pattern of activity, which may reflect the use of different mnemonic strategies across the two groups or, alternatively, it may reflect a functional compensation for neuropathological changes associated with Alzheimer's disease (Gould et al., 2005). Fowler and co-workers reported that a 6-month decline in the PAL performance of patients with mild cognitive symptoms predicts later progression to AD (Fowler et al., 1997, 2002). The poor performance shown by patients with questionable dementia in the PAL test may be the result of a loss of muscarinic cholinergic receptors and/or to an impairment of the cholinergic neurotransmission in the parahippocampal region (Fowler et al., 2002; Taffe et al., 2004).

The performance of both AD and MCI patients was substantially impaired in the delayed matching to sample (DMS). The delayed matching to sample test mainly assess the cognitive functions of the temporal regions, a locus well-known to be involved early in the pathology of Alzheimer's disease (Twamley et al., 2006). A significant impairment was also found in the rapid visual processing (RVP) test as well, which suggests the impairment of sustained attention. Though it is primarily a test of visual sustained attention, it also requires both selective attention and working memory for successful execution. The impairment of these cognitive domains is well documented in Alzheimer's disease (Rizzo et al., 2000; Jackson and Owsley, 2003). The spatial span (SSP) test, like the spatial working memory (SWM) task, is sensitive to working memory impairment and thus to frontal lobe functions (Owen et al., 1995); in the present study both MCI and AD patients had dysfunction in this domain. The spatial recognition memory (SRM) task performance, involving the neural systems of the medial temporal, inferotemporal and several frontal regions was also significantly impaired in both patient groups (Johnsrude et al., 1999).

AD, but not MCI, patients had a significant impairment in two attentional tasks: matching-to sample (MTS), reaction time (RTI) tasks, and in the pattern recognition memory (PRM) test, involving the activity of posterior brain regions (Owen et al., 1995) which may suggest that these cognitive domains are better preserved in the earliest phase of AD. In the present study we were unable to find any significant impairment in a test of executive function (Stockings of Cambridge — SOC) in both AD and MCI patient group. As executive dysfunction is usually present in the early stages of AD (Arnaiz and Almkvist, 2003; Twamley et al., 2006), this negative result may be related to the younger age of both AD and MCI patients in the present study.

Long before the onset of clinical dementia, neuropathological changes are already present in mesial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex), areas critical for long-term episodic memory (Dubois and Albert, 2004). Amnestic mild cognitive impairment (MCI) may be a prodromal state for Alzheimer's disease. While the diagnosis of MCI is ultimately based on clinical judgement, it may be supported by self-reported difficulties, informants' reports about memory loss problems, and impaired psychometric test performances. In the present study CANTAB was used to compare cognitive deficits in a group of AD and MCI patients in order to assess whether CANTAB can be a useful tool to detect the early stages of Alzheimer's dementia. The obtained results support previous findings that both AD and MCI patients had a significantly impaired performance in the Paired Associate Learning (PAL) test, showing a dysfunction of the medial temporal lobe (Blackwell et al., 2004; Ribeiro et al., 2006; Alladi et al., 2006). This impairment found in both patient

Table 2
The median *Z*-scores of the CANTAB tests compared to healthy individuals in the AD group ($n=15$) and MCI group ($n=25$)

| CANTAB tests | AD ($n=15$) | | MCI ($n=25$) | |
|---|---|---|---|---|
| | Median *Z*-scores | Significance (*P*) | Median *Z*-scores | Significance (*P*) |
| Paired associate learning (PAL) | −7.196 | <0.05 | −2.942 | <0.001 |
| Spatial recognition memory (SRM) | −2.201 | <0.001 | −2.061 | <0.001 |
| Spatial working memory (SWM) | −0.968 | <0.01 | −0.8871 | <0.001 |
| Rapid visual processing (RVP) | −2.735 | <0.001 | −2.101 | <0.001 |
| Spatial span (SSP) | −1.212 | <0.01 | −0.755 | <0.001 |
| Stocking of Cambridge (SOC) | −0.5713 | n.s. | −0.2675 | n.s. |
| Matching-to-sample (MTS) | −4.103 | <0.05 | −0.2235 | n.s. |
| Reaction time (RTI) | −1.109 | <0.01 | −4.520 | n.s. |
| Pattern recognition memory (PRM) | −1.942 | <0.01 | −0.3715 | n.s. |
| Delayed matching to sample (DMS) | −2.641 | <0.001 | −1.111 | <0.05 |

n.s.=not significant.



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groups may suggest that the impaired performance in the PAL test can serve as a marker for preclinical Alzheimer's disease, and thus could be a useful tool to detect AD and also an objective marker for the initiation of treatment in an early phase of the development of AD. As several other domains were also affected in MCI, further studies would help to characterize the cognitive dysfunction profile in preclinical AD, which could provide a more sensitive and specific approach to the early detection and monitoring of progress of the disorder.

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