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EXECUTIVE FUNCTIONS DEFICIT IN MILD COGNITIVE IMPAIRMENT

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Running title: Executive functions deficit in MCI

Key words: Mild Cognitive Impairment; Neuropsychology; Attention; Executive functions; Memory; Alzheimer's disease.

Abstract

Objective: To investigate whether patients diagnosed as amnesic mild cognitive impairment (MCI) have also impairment in attention/executive functions and, therefore to clarify whether all subcomponents of executive control are equally affected in MCI.

Background: MCI refers to the transitional state between normal ageing and dementia.

Amnesic MCI is characterized by impaired episodic memory, although subtle impairment of executive functions has been noted on neuropsychological tests.

Methods: We investigated 20 MCI patients and 20 normal controls using episodic memory, attention/executive functions, language and praxis tests.

Results: MCI patients had a significantly lower scores on all measures of the Free and Cued Selective Reminding Test ($p < 0.05$ to 0.01) than controls. Furthermore MCI had a greater number of perseverations ($p < 0.01$) on Modified Card Sorting Test and the lowest performance on the Stroop test ($p < 0.02$).

Conclusion: Our findings showed impairment in episodic memory performance in MCI as compared to that of controls. In addition, MCI patients had problems with response inhibition, switching and cognitive flexibility which encompass various aspects of executive functions. This suggests that MCI may be identified by using a more detailed procedure for the assessment of cognitive decline than the evaluation of memory alone.

Introduction

The recent developments in drug treatments for Alzheimer's disease (AD) have highlighted the importance of early diagnosis and the need to characterize the cognitive profile of the earliest stages of the disease.

Recent research has identified a transitional state between the cognitive changes of normal aging and AD, known as mild cognitive impairment (MCI).^{1,2} Patients with MCI have a memory impairment that is higher than that expected for their age, yet they do not meet commonly accepted criteria for dementia or AD because their cognitive deficits are limited to memory alone and their everyday abilities are preserved. Although MCI can present a variety of symptoms, when memory loss is the predominant symptom it is termed "amnesic MCI" and the risk is higher for the development of AD.² These patients progress to AD at a rate of 10% to 15% per year, as compared to elderly individuals without MCI, who convert at rates of 1% to 2%.¹ However, subsequent work has also indicated that MCI is heterogeneous in its clinical presentation and should be considered in a broad clinical context.³ The principal cognitive impairment can be amnesic, single nonmemory domain or involving multiple cognitive domains (with or without a memory impairment).

Several studies have suggested that an impairment of memory is most common in amnesic MCI and is the fundamental aspect of cognition to evaluate.⁴ Petersen et al.¹ reported verbal episodic memory performance in an MCI group that was as impaired as that seen in mild AD. However, the same MCI group's performance on measures assessing other cognitive domains (naming, executive functions, etc.) was equivalent to that of healthy older controls.

Other studies of MCI report cognitive deficits similar to those described by Petersen and colleagues.^{5,6}

However, in recent years, the literature has reported that, while memory is the hallmark of patients with amnesic MCI, they are impaired on a variety of tasks that have commonly been considered a measure of executive functions.⁷ Executive functions are encompassing a number of cognitive abilities which generally have been conceptualized as controlling or guiding behavior in a top-down fashion such as decision-making, planning, self monitoring, and behavior initiation, organization and inhibition.⁸ Within this context Ready et al.⁹ demonstrated that increased executive impairment is common in patients with amnesic MCI and is evident in patients who are not functionally impaired. Similarly, Perry et al.¹⁰ reported particular problems with response inhibition and attentional switching in a group of patients who were only impaired on episodic memory tests. Finally, Rapp et al.¹¹ reported recently that tasks requiring executive control are significantly affected in the preclinical phase of AD and are reliable predictors of the disease before diagnosis. The results of these studies emphasised the importance of attention and executive function in MCI patients. However, it must be pointed out that variability across studies in both tasks used to examine aspects of executive function, and in the MCI definition, makes it difficult to determine which aspects of executive control are affected in MCI. Consequently, we selected executive tasks more “universally” accepted like those mentioned in the above-cited studies. The objective was to avoid to further clouding the issues by introducing additional measures.

The aims of our study were to investigate whether patients diagnosed as amnesic MCI have also impairment in attention/executive functions and, therefore to clarify whether all subcomponents of executive control are equally affected in MCI.

Materials and methods

Participants

Subjects were selected among patients who sought consultation at the Broca Geriatric Day Care Hospital in Paris, between January 1999 and December 1999, because of memory problems or other symptoms of cognitive deterioration. The evaluation procedure consisted of detailed medical history, physical and neurological examinations, psychiatric and cognitive evaluations, laboratory tests, and brain computed tomography (CT) and/or magnetic resonance imaging (MRI). The Clinical Dementia Rating scale (CDR)¹² was also completed. The psychiatric evaluation included a semistructured interview and the Geriatric Depression Scale (GDS).¹³ Cognitive status was evaluated by the Mini Mental State Examination (MMSE)¹³ and a screening neuropsychological battery previously described.^{15,16} Laboratory workup included complete blood count and differential, serum electrolytes and glucose, liver and renal function tests, thyroid function tests, VDRL, serum B12 and folate levels. All available information was evaluated by an experienced geriatrician, neurologist (who is also trained in brain imaging), and neuropsychologist. Data from patients with coexisting dementia and major depression (DSM-IV)¹⁷ were not used. Subjects were included in the study after classification into MCI or NC diagnostic categories.

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MCI group: Twenty consecutive elderly subjects with cognitive deficit failed to meet DSM-IV¹⁷ criteria for Dementia because the mild cognitive impairment did not interfere significantly with their daily activities. The criteria utilized for the selection of the MCI patients were those proposed by the Mayo Clinic Alzheimer's Disease Center).¹⁸ The 20 patients in this group had: 1) memory complaint by the patient or a reliable informant, 2) normal global cognitive function (MMSE >26), 3) objective memory impairment as demonstrated by scores of more than 1.5 SDs below age- and education-matched norms, as previously developed),¹⁹ 4) generally preserved functional capacity and activities of daily living both by history and by functional scale (CDR= 0.5) assessment and 5) no evidence of any neurological (verified with CT or MRI, (6 and 14 respectively)), psychiatric, or medical disorder nor of drug use that could induce cognitive deterioration. To avoid subcortical vascular lesions we excluded from the study patients that presented any of the following: history of cardiac disease or minor stroke events; clinical course with abrupt deterioration of cognitive function, stepwise decline, or fluctuation; and evidence of relevant CVD by brain imaging (CT or MRI findings of single or multiple small subcortical infarcts and extensive white matter changes). In addition, patients with coexisting cognitive impairment and major depression (DSM IV criteria)¹⁷ were excluded from the study.

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Normal controls group: To compare the neuropsychological performances we composed a control group of 20 elderly subjects without history or symptoms of psychiatric or neurological disease and with integrity of their cognitive functions. However they had no abnormalities on in depth clinical, neurological, psychiatric and neuropsychological

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examinations, ~~All of the controls underwent brain CT.~~ They were matched to patient groups according to age, sex and educational level.

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Neuropsychological Assessment

Cognitive functions were evaluated in all participants by a comprehensive neuropsychological battery consisting of subtests and modified short forms of commonly used neuropsychological measures. The neuropsychological assessment was blinded to the clinical diagnosis. Short-term memory was examined by the Digit Span (forward) of the Wechsler Adult Intelligence Scale (WAIS)¹⁹ and the Corsi Block Tapping Test.²⁰ Episodic long-term memory was assessed with the Buschke Free and Cued Selective Reminding Test (FCSRT),²¹ assessing free recall (number of items retrieved over three learning trials), total recall (number of words recalled with free and cued procedures over three learning trials), recognition, and the delayed free and total recall.²² Attention and executive functions were tested by the Bells test)²³ (assessing the time to cross out all bells), the Digit Symbol test,¹⁹ assessing the number of symbols correctly drawn for 90 seconds, the Trail Making Test part A (TMT-A) and part B (TMT-B)²⁴ (assessing the time to correctly rely all items in each of the trials), the Modified Card Sorting Test (MCST)²⁵ (assessing number of categories achieved and perseverative errors), the Stroop Color Interference Test (SCIT),²⁶ (assessing, in the third part, the number of items correctly named in 45 seconds). Language abilities were assessed by the Fifteen Item Subset of Boston Naming Test (BNT),²⁷ the semantic Verbal Fluency²⁸ (categories animals, assessing number of category exemplars produced in 60 seconds) and the phonemic Verbal Fluency²⁸ (letters F, assessing

number of words produced with each letter in 60 seconds). Visuospatial abilities were evaluated by the constructional praxis (copy five complex designs).²⁹

Statistical Analysis

Statistical analyses were performed with the SPSS 7.5 software package. We performed multivariate analysis of variance (MANOVA) on the dependent variables of each test with the group factor to eliminate variations that cannot be attributed to the cognitive items under study. An analysis of variance (ANOVA) on each test variable was performed separately.

Results

Demographic characteristics of the patients and controls were presented in table 1. The ANOVA was used to examine group differences in age and education scores. There were no significant differences between the patients and controls on these variables. There were also no significant differences on gender ($\chi^2 = 0.5$; $p = 0.46$). With regard to MMSE, the ANOVA showed that MCI patients differed significantly from normal controls.

Table 1 here

The neuropsychological performance of the two groups included in this study is shown in Table 2. Multivariate analysis of variance revealed a significant difference between groups on neuropsychological tests, Wilks lambda =0.203, F=3,368, p<0,006.

With regard to memory tasks, the ANOVA showed that MCI patients differed significantly from normal controls on all the measures of the FCSRT (p < 0.05 to 0.0001; see table 2 for F values). Short-term memory, as measured by the forward Digit Span and the Corsi Block Tapping test, was not impaired in the MCI group relative to controls.

Table 2 here

In terms of tasks which encompass various aspects of attention and executive functions, ANOVA revealed that performance on the Stroop test and MCST, was significantly impaired in MCI group relative to controls. However, no significant difference was found between patients and controls on Bells test, Digit symbol test, Trail Making test A and B.

With regard to language tasks, intergroup comparisons indicated that patients performed within normal limits on the category and phonemic Verbal Fluency test and the BNT. Similarly, no significant difference was found between patients and controls on Constructional Praxis as measured by the copy of complex designs.

Discussion

Our findings show that in addition to the impairment in the anterograde verbal episodic memory performance MCI patients had problems with response inhibition, switching, cognitive flexibility and abstract thinking which encompass various aspects of executive function. The performance on measures assessing all other cognitive domains (short-term memory, language abilities, constructional praxis, etc.) was comparable to that of normal controls.

Despite this was not the main goal of our study, we would like to stress on the benefits of the Buschke's FCSR test²¹ usage, in spite of the studies that examined memory functioning in MCI using free recall measures.^{1,2} Our findings show that MCI patients recalled significantly fewer words on immediate and delayed free recall than did matched control participants and show, in addition, lesser efficacy of cued recall. Similar results were obtained by Grober et al.³⁰ who investigated learning and retention in participants who later developed AD. Considered together, our findings with those of Grober et al.³⁰ indicate that detection of MCI and very early AD may be best accomplished by using robust learning tests that control cognitive processing.

Deleted: In accordance with the selection criteria we found that MCI patients showed significant impairments on episodic memory measures in comparison to controls. However, a considerable number of studies that have examined memory functioning in MCI used free recall measures.^{1,2} In the present study, episodic memory was assessed with the Buschke's FCSR test,²¹ a test that maximizes learning by inducing deep semantic processing and by controlling study and test conditions. Because this test coordinates encoding and retrieval for maximum recall, genuine memory deficits due to impairment of specific memory processes can be distinguished from apparent memory deficits due to use of inefficient strategies or impairment of other cognitive processes. The results

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In addition to the severely abnormal episodic memory performance, we found a significant executive functions deficit in the MCI group as assessed by the Stroop test and the Modified WCST (number of errors and perseverations). Both tests are well known and validated executive tasks measuring the ability to inhibit irrelevant responses, the set

shifting and cognitive flexibility. These findings are in agreement with the results of Nagahama et al.³¹ who reported more frequent perseverative errors by the MCI patients on modified WCST and argued that this reflects an aspect of executive dysfunction in MCI.

Our results also support the suggestion of Perry et al,¹⁰ that some subcomponents of executive control, such as the selective attention and response inhibition may be particularly sensitive to the effect of MCI, while other attentional/executive processes may be relatively preserved. In fact, our patients showed particularly impaired performance on tasks requiring resolution of competing response tendencies and target discrimination with relatively preserved performance on tasks of sustained and divided attention. Like Perry et al,¹⁰ our study has shown that tasks of selective attention such as the Stroop Test are the most sensitive for picking up attention deficits in MCI or very mild AD patients. Some authors suggest that executive deficits appear early in AD but the initial stage of the disease, known as MCI is characterised by amnesia alone with profound loss of episodic memory, despite intact executive functions.¹⁰ Longitudinal studies employing neuropsychological assessment in small groups of subjects have suggested that, following the amnesia-only phase, deficits in executive functions and/or semantic memory arise before all domains of cognitive processing become affected.³² Other studies have shown both episodic memory and executive function tasks to be predictive of later onset of AD,³³ and some,³⁴ indeed report executive functions to be equally predictive for the later development of AD. Thus, although an episodic memory deficit is generally considered to be the first sign of AD, these longitudinal results support a multiple pattern of deterioration prior to AD. Similarly, recent studies show, that when the clinical syndrome of MCI evolves on a neurodegenerative basis, the multiple-domain type of MCI has a less favorable prognosis than the amnesic type and may represent a more advanced prodromal stage of dementia.^{35,36} Our results of profound memory impairment in association with executive functions deficit in “amnesic MCI” suggest that more extensive examination of executive functions may help the early identification of incipient **AD**.

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Conversely to some previous studies,^{37,38} we did not find significant difference between MCI and NC on verbal fluency test, whereas MCI patients were expected to perform poorer at least on the semantic fluency task. Murphy et al³⁸ suggested that the reduced efficiency in accessing semantic fluency indicates that the early neuropathology of AD may extend beyond the hippocampus to include cortical areas supporting semantic memory. The most likely explanation for the sparing of performance of fluency tasks in our MCI patients concerns the difference of the overall cognitive impairment (MMS score) between our patients and those of others. Our hypothesis is that our patients' semantic memory is still intact because of the earlier stage of impairment. Supporting our suggestion are the normal results of the BNT.

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While it is generally agreed that early memory impairment in MCI is associated with entorhinal and medial temporal lesions early in the course of the disease,³⁷ it is very difficult to explain the early impairment of executive functions in terms of direct early involvement of frontal regions. It must be stressed, however, that the precise anatomical correlates of executive functions are still a matter of debate. Several authors,³⁸ have proposed that early disconnection of the cortico-cortical tracts is the cause of the executive impairment in AD. If so, then executive functions appear sustained by a distributed cortical neural network rather than by a unique frontal region and is very "sensitive" to disruption.

This view is supported by the results of the recent functional MRI study, which segregate different network components underlying the Wisconsin CST (WCST).³⁹ The data revealed the entire neural network underlying WCST performance, including the right ventrolateral and dorsolateral prefrontal cortices, and the anterior cingulate cortex (ACC). Moreover, recent study of functional MRI and Stroop test offers concrete evidence of prefrontal circuit activation including the left medial frontal gyrus, left dorsolateral prefrontal cortex and bilaterally in the ACC.⁴⁰ In addition, a study of schizophrenia with the WCST link poor performance at the test to reduced activation in the ACC.⁴¹

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A recent PET study by Mosconi et al.⁴² in MCI ApoE carriers subjects at higher risk of conversion to AD showed rCMRglc reduction within frontal areas, such as the ACC and inferior frontal cortex. Here, a symptomatic shift from MCI to AD may be related to the

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appearance of this frontal metabolic dysfunction, which could ensue from anterior-posterior cortico-cortical disconnection, which supports the hypothesis of early executive impairment. A supplemental explanation of the appearance of attentional deficits in AD comes from the damage to the nucleus basalis of Meynert, which provides the major cholinergic innervation to the cortex, and which is affected by early pathological changes, and so may be responsible for attentional impairments.

There are some limitations to the current study. We cannot be certain about our rate of diagnostic misclassification because of the lack of neuropathological confirmation of our clinical diagnoses. However, the detailed clinical and neuropsychological assessments, the use of neuro-imaging to clarify cerebral abnormalities and, finally, the use of a trained research team consisting of a neuropsychologist, geriatrician, and neurologist (also trained in brain imaging) reasonably limited the chance for diagnostic misclassification. In our attempt to select homogeneous populations as much as we could, we paid special attention not to include in our study patients with subcortical vascular lesions or depression. The small number of our groups may also be a limitation, because of the lack of power in statistical analysis. When checking our results in addition to the above described highly reliable results of the Stroop Test and the MCST, we find tendency for statistical significance only in TMT-B. However, even if the TMT-B results become significant in larger groups study, its findings will not contradict with our suggestion of predominantly selective attention and response inhibition deficit in MCI patients.

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In conclusion, our results show that executive functions are impaired in MCI patients.

Executive functions deficits appear predominantly in tasks requiring resolution of competing response tendencies, cognitive flexibility and self-monitoring. These results suggest that MCI should be identified by using a more detailed procedure for the assessment of cognitive decline than the evaluation of memory alone. The possible relationship between impaired executive functions and incipient dementia in individuals with MCI, and the question of whether detecting executive deficits could improve

prediction of the conversion from MCI to AD, remains to be investigated in follow-up studies.

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Table 1. Demographic characteristics of patients with MCI and normal controls

	NC (n = 20)	MCI (n = 20)	F	p
Gender W/M	6/14	4/16		0.47
Age, years	73.3 (7.0)	73.2 (8.0)	0.0004	0.983
Education, years	12.8 (3.3)	12.1 (3.1)	0.471	0.496
MMSE	29.5 (0.5)	28.95 (1.1)	4.430	0.042

Values are means (SD); NC = Normal controls; MCI = mild cognitive impairment;

MMSE = Mini Mental State Examination.

Table 2. The neuropsychological performance of the two groups and the results of ANOVA on each test

	NC	MCI	F	p
Memory				
Digit Span	6.0 (1.3)	5.9 (1.0)	0.019	0.8921
Corsi Test	4.9 (0.9)	4.6 (1.0)	0.691	0.4109
FCSRT (free recall)	30.9 (5.7)	21.1 (4.9)	34.051	<0.0001
FCSRT (total recall)	47.0 (0.9)	41.2 (4.6)	30.494	<0.0001
FCSRT (free delayed recall)	13.1 (2.4)	8.9 (2.4)	38.824	<0.0001
FCSRT (total delayed recall)	15.9 (0.3)	15.0 (1.0)	12.068	0.0013
FCSRT (recognition)	15.95 (0.2)	15.6 (0.7)	4.774	0.0351
Attention/Executive function				
Trail Making Test A (time)	54.4 (13.2)	61.1 (21.0)	1.475	0.2320
Trail Making Test B (time)	120.1 (57.5)	157.2 (70.8)	3.313	0.0766
Bell test (time)	142.4 (41.2)	151.5 (50.2)	0.386	0.5382
Digit Symbol	41.2 (10.3)	39.4 (12.5)	0.248	0.6215
Stroop Test (interference)	37.1 (9.6)	28.6 (10.9)	6.749	0.0133
MCST (categories)	5.9 (0.4)	5.6 (0.7)	2.974	0.0927
MCST (perseverations)	0.4 (0.7)	2.2 (2.7)	7.445	0.0096
MCST (errors)	1.7 (2.2)	5.2 (4.9)	8.321	0.0064
Praxis				
Copy designs	13.7 (0.8)	13.6 (1.0)	0.123	0.7282
Language				
Boston Naming Test	14.9 (0.4)	14.8 (0.4)	0.165	0.6867
Verbal Fluency (animals)	20.1 (4.5)	19.7 (4.2)	0.086	0.7714
Verbal Fluency (letter F)	13.4 (4.0)	11.6 (4.1)	1.832	0.1839

Values are means (SD); FCSRT = Free and Cued Selective Reminding Test; MCST = Modified Card Sorting Test.