ORIGINAL COMMUNICATION

Facundo Manes
Cecilia Serrano
María L. Calcagno
Julian Cardozo
John Hodges

Accelerated forgetting in subjects with memory complaints
A new form of Mild Cognitive Impairment?

F. Manes, MD (✉) · J. Cardozo
Institute of Cognitive Neurology (INECO)
Castex 3293 (1425)
Buenos Aires, Argentina
E-Mail: fmanes@neurologiacognitiva.org

F. Manes
Institute of Neuroscience
Favaloro Foundation, Argentina

C. Serrano
Centro de Educación Médica e
Investigaciones Clínicas „Norberto Quirno"
Buenos Aires, Argentina

M. L. Calcagno
School of Pharmacy and Biochemistry
University of Buenos Aires, Argentina

J. Hodges
MRC Cognition and Brain Sciences Unit
Addenbrooke's Hospital
Cambridge, UK

J. Hodges
University of Cambridge Neurology Unit
Addenbrooke's Hospital
Cambridge, UK

F. Manes and C. Serrano contributed
equally to this work.

■ **Abstract** A study was carried out to investigate accelerated forgetting of new verbal and visual material in participants complaining of memory loss, individuals with Mild Cognitive Impairment (MCI) and controls. All groups were evaluated with a standard neuropsychological battery and two tests of delayed recall 6 weeks apart for the experimental tasks. Individuals with memory complaints, but not MCI, performed normally compared to controls on immediate and 30 minute recall, but showed a striking impairment in verbal and visual memory after 6 weeks. Accelerated forgetting may go undetected on standard neuropsychological evaluation in some patients complaining of memory problems.

■ **Key words** memory complaint · mild cognitive impairment · accelerated forgetting

Introduction

Subjects with amnesic Mild Cognitive Impairment (aMCI) have abnormal memory function for their age and education level, do not meet the criteria for Alzheimer's disease but have a high rate of conversion over subsequent years. The accurate categorization of cases with MCI is clearly dependent upon the sensitivity of memory tests used in the standard neuropsychological evaluation.

A clinically distinct subgroup of individuals with complaints of everyday memory failures and accelerated forgetting of new information (such as the content of conversations and books), yet normal scores on standard anterograde memory tests have come to our attention. One possible explanation for the contrast between their subjective reports and their normal memory test scores is that they have accelerated forgetting of information rather than poor initial encoding: a profile that has been reported in the context of temporal lobe epilepsy and transient epileptic amnesia [1, 2].

The aim of the present study was, therefore, to test the hypothesis that accelerated forgetting of new material may underline the complaints of some patients complaining of memory problems. A long-term forgetting experiment was carried out to investigate accelerated forgetting of verbal and visual material over a 6 week period in subjects who met with criteria for aMCI, individuals with memory complaints with good performance on standard anterograde memory tests and controls.

Patients and methods

■ Subjects

Subjects were selected from the Memory Clinic at the Institute of Cognitive Neurology (INECO) and the Raúl Carrea Institute, Buenos Aires, Argentina, where the ethics committees approved and supervised the project in accordance to international standards. Patients were classified into three groups: a) *Complaint group:* 10 individuals with complaints of memory loss with normal cognitive evaluation; b) *Amnestic Mild Cognitive Impairment group (aMCI group)* (for a review see [5]): 7 individuals who complained of memory loss with objective memory impairment (memory > 1.5 SD) without impact on aspects of daily living and c) *Control group:* 9 healthy individuals. None of the participants had a history of drug or alcohol use, head trauma, or previous neurological or psychiatric disorders. Illiterate individuals or those with less than 12 years of education were excluded, as well as subjects with anxiety or depression or those whose MRI scans revealed neuroradiological findings of significant vascular disease. All subjects gave informed consent prior to the beginning of the experiment.

■ Neuropsychological evaluation

Standard neuropsychological evaluation

The Addenbrooke's Cognitive Examination (ACE) and the Mini-Mental State Examination (MMSE) were used as general measurements of cognitive decline. The ACE is a 100-point test battery that assesses six cognitive domains [3]. The standard neuropsychological battery is shown in Table 1.

Experimental evaluation

A small battery of tests suitable for investigating long-term forgetting was given to each participant (see [1]).

Logical memory: story recall and recognition

Participants were asked to listen to two stories and recall them from memory immediately, at 30 minutes and at 6 weeks. One point was given for each correctly recalled item.

Rey complex figure

Subjects drew the complex figure and were asked to recall it at 30 minutes and 6 weeks.

■ Statistical analysis

Standard tests were compared by means of one-way analysis of variance (ANOVA) if variance homogeneity was reached. If not, the Kruskal-Wallis nonparametric analysis of variance was used. Data obtained from the forgetting tests were analyzed by means of a two-way ANOVA with a between subjects measure of 'group' and a repeated measure of 'time'. Main effects and interactions were investigated, after which simple effect tests were conducted to evaluate differential behavior of groups. When a difference was detected between means, a post hoc test was carried out: Tukey test with a 5% global probability level. SPSS 10.0 statistical software was used.

Results

Demographic variables and results of the standard neuropsychological evaluation are shown in Table 1. MCI subjects showed impaired immediate and 30-minute recall compared to controls. Recognition memory was also impaired. Their only other significant deficit was on the Boston Naming task with respect to the control and complaint groups. The complaint group performed similarly to the control group on all tests.

■ Experimental tests

Verbal logical memory recall

ANOVA revealed main effects of group ($F_{2,23} = 15.2$, $p < 0.001$) and time ($F_{2,46} = 89.9$, $p < 0.001$) as well as a highly significant interaction between time and group ($F_{4,46} = 4.385$; $P < 0.005$). As illustrated in Fig. 1 post hoc

Table 1 Demographic variables and basal tests. Data are shown as mean (SD)

	Control (n = 9)	Complaint (n = 10)	MCI (n = 7)	F	P
Age	65.44 (6.88)	63.60 (8.69)	70.57 (10.50)	$F_{2,23} = 1.38$	0.272
Education (years)	15.22 (2.73)	17.80 (3.74)	17.29 (3.77)	$F_{2,23} = 1.45$	0.256
MMSE	29.22 (1.09)	29.20 (0.79)	28.57 (1.40)	$F_{2,23} = 0.90$	0.422
ACE	95.11 (4.99)	96.90 (2.13)	92.00 (5.57)	$F_{2,23} = 2.68$	0.09
Digits span	11.11 (1.27)	10.10 (1.52)	9.71 (1.80)	$F_{2,23} = 1.87$	0.176
TMTA	39.00 (9.38)	39.90 (8.79)	49.57 (18.71)	$F_{2,23} = 1.74$	0.198
Clock	7 (0)	7 (0)	6.86 (0.38)	$H = 0.30^a$	0.257
Cubes	6 (0)	6 (0)	5.71 (0.76)	$H = 0.30^a$	0.257
BNT	54.89 (1.76)	52.60 (3.44)	48.14 (5.05)	$F_{2,23} = 7.36$	0.003*c
Token test	95.33 (0.87)	96.00 (0)	95.57 (0.79)	$H = 2.79^a$	0.077
WCST	6.00 (0)	6.00 (0)	5.71 (0.49)	$H = 1.21^a$	0.059
TMTB	81.89 (12.94)	82.10 (19.76)	142.00 (64.86)	$H = 5.22^a$	0.073
Beck Depression Inventory	3.67 (1.80)	4.40 (1.58)	5.29 (1.60)	$F_{2,23} = 1.86$	0.178

* Significant; [a] Kruskall-Wallis test; [b] MCI differs from Complaint; [c] MCI differs from Control and Complaint; [d] Control immediate differs from 30 minutes; [e] Complaint immediate differs from 30 minutes

tests revealed highly significant difference among the groups for each of the three time-periods ($F_{2,69} = 8.87$; $P < 0.001$ for immediate; $F_{2,69} = 14.88$; $P < 0.001$ for 30 minutes; $F_{2,69} = 14.44$; $P < 0.001$ for 6 weeks). The post hoc tests revealed that the MCI performed significantly worse than controls and the memory complaint groups at immediate and 30 minute recall; with controls and memory complaint groups performing equivalently. At 6 weeks, however, both the MCI and the memory complaint group performed worse than controls, with no statistically significant difference between the MCI and memory complaint groups.

Rey complex figure

As shown in Fig. 1, the primary analysis revealed main effects of group ($F_{2,22} = 10.6$; $p < 0.001$) and time ($F_{2,44} = 119.7$; $p < 0.001$) as well as a significant interaction between group and time ($F_{4,46} = 2.77$; $P < 0.05$). Post hoc tests confirmed that this reflected differences between the three groups for immediate ($F_{2,69} = 7.17$; $P < 0.01$), 30 minute ($F_{2,69} = 6.68$; $P < 0.01$) and 6 week recall ($F_{2,69} = 13.82$; $P < 0.001$). While the MCI group showed significantly poorer recall than the controls and memory complaint groups, both at immediate and at 30 minute recall, the performance of the control and complaint groups did not differ. At 6 weeks, however, the memory complaint group, as well as the MCI cases, performed significantly poorer than the controls with no evidence of a statistical difference in scores between the MCI and memory complaint groups.

Fig. 1

Discussion

We have shown that a group of memory clinic attendees who perform normally in standard neuropsychological tasks, and do no therefore meet criteria for aMCI, have accelerated forgetting with extremely weak memory, for both verbal and visual material, when tested at 6 weeks. The degree of memory deficit seen at 6 weeks was in fact indistinguishable from cases fulfilling the criteria for MCI. These results confirm the observations made by the patients and suggest that a more extended cognitive assessment may be useful in some individuals presenting with memory complaints, yet normal performance on standard memory tests.

While one limitation of our study was the relatively small sample size, the effects were statistically robust and clearly warrant investigation in a larger group. It would also be valuable to identify just how quickly patients forget: here we tested recall at 6 weeks (a time-period similar to that used in studies of forgetting in epilepsy), but it is likely that the patients would have shown a significant loss of memory even if tested at a shorter time interval.
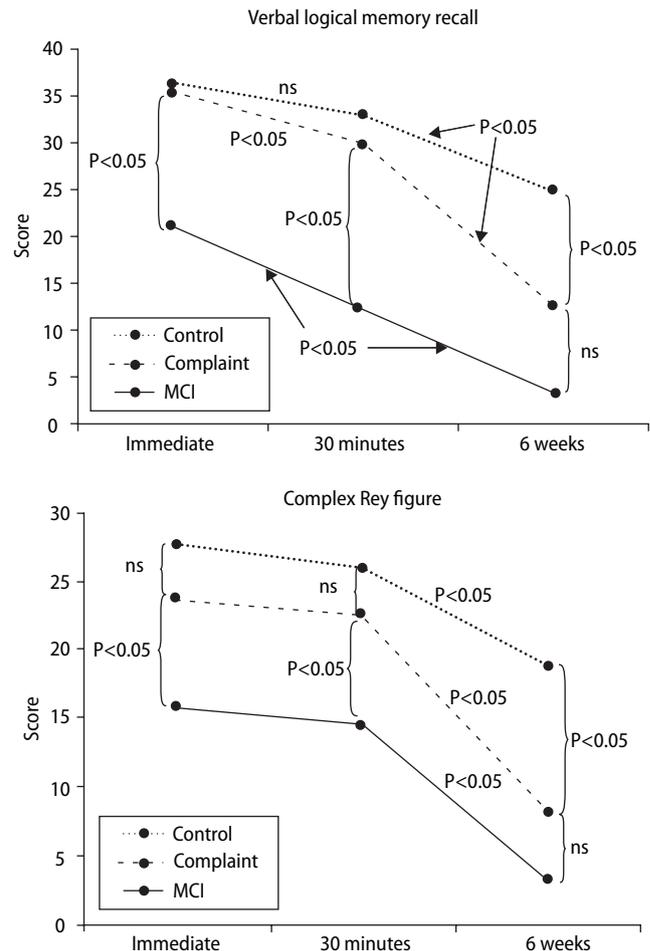
We are not claiming that all memory clinic attendees with normal performance cognitive tests have long-term forgetting. Analysis of individual patient's performance showed that some memory complainers have accelerated forgetting ($n = 6$) while others were normal ($n = 4$). Further research with larger samples should address the question of what percentage of subjects with memory complaints demonstrate this phenomenon. Accelerated forgetting may constitute a new sub-form of MCI. It is interesting to speculate on whether such patients might have clearly identifiable symptoms. We hypothesize that they might be aware of reasonable retention of new memories over a short period but then pathologically fast fading of these new memories over days or weeks.

A further question of interest is why the aMCI and memory complaint cases show accelerated forgetting. While the MCI participants had less to remember over time, given their poorer initial encoding and/or consolidation of information, the memory complaint group showed similar levels of learning to that seen in controls at immediate and 30 minute recall. It has been shown

that patients with temporal lobe epilepsy [1] and with transient epileptic amnesia [2] demonstrate accelerated forgetting over a similar time period: it has been proposed that accelerated forgetting results from either repeated seizure activity that results in an inability to reinstate new memories or underlying hippocampal pathology. There was no clinical evidence of seizure disorder in our memory complaints group. It seems more probable that it reflects subtle dysfunction of the extended medial temporal lobe circuit, which includes the retrosplenial cortex and is shown to be hypometabolic in aMCI [4], thus, affecting long-term consolidation.

In summary, our study is the first to show memory impairments – as measured by accelerated forgetting – in cases who do not fulfill criteria for aMCI. These findings highlight the importance of tests of forgetting in the clinical setting and the need to develop more sophisticated criteria for the early diagnosis of MCI. Further studies with follow-up will be important to establish the true status of the accelerated forgetting subgroup and particularly how many of these patients develop dementia in the long term.

References

1. Blake R, Wroe S, Breen E, McCarthy R (2000) Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. Brain 123:472–483
2. Manes F, Hodges JR, Graham KS, et al. (2001) Focal autobiographical amnesia in association with transient epileptic amnesia. Brain 124:499–509
3. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR (2000) A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology 55:1613–1620
4. Nestor PJ, Fryer TD, Ikeda M, Hodges JR (2003) Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). Eur J Neurosci 18:2663–2667
5. Dubois B, Albert ML (2004) Amnestic MCI or prodromal Alzheimer´s disease? The Lancet, Neurology 3:246–248