

PROSPECTIVE AND RETROSPECTIVE MEMORY IN MILD ALZHEIMER'S DISEASE

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Abstract – Objective: To study prospective and retrospective memory in patients with mild Alzheimer's disease (AD). **Method:** Twenty mild AD and 20 matched normal control subjects were included. Diagnosis of AD was based on DSM-IV and NINCDS-ADRDA criteria, using CDR 1 and MMSE scores from 16 to 24 for mild AD. All subjects underwent retrospective (Rey Auditory Verbal Learning Test, RAVLT) and prospective memory tests (the appointment and belonging subtests of the Rivermead Behavioral Memory Test, RBMT; and two tests made to this study: the clock and the animals test), as well as MMSE, neuropsychological counterproofs, and Cornell Scale for Depression in Dementia. The data was analyzed with Wilcoxon test and Spearman correlation coefficient. **Results:** AD patients performed worse than controls in prospective and retrospective memory tests, with poorer performance in retrospective memory. There was no correlation between prospective memory and attention, visual perception, executive function, or depression scores. **Conclusion:** Prospective and, in higher degree, retrospective memory are primarily and independently impaired in mild AD.

KEY-WORDS: prospective memory, Alzheimer's disease, dementia, neuropsychological tests.

Memória prospectiva e retrospectiva na doença de Alzheimer leve

Resumo – Objetivo: Estudar a memória prospectiva e retrospectiva em pacientes com doença de Alzheimer (DA) leve. **Método:** Vinte pacientes com DA leve e 20 sujeitos controles normais pareados foram incluídos. O diagnóstico de DA baseou-se nos critérios DSM-IV e NINCDS-ADRDA, usando CDR 1 e escores do Mini-Exame Mental de 16 a 24 para DA leve. Todos os sujeitos foram submetidos a testes de memória retrospectiva (Teste de Rey para Aprendizado Auditivo-Verbal) e prospectiva (os testes da consulta e do pertence da Bateria Comportamental de Memória do Rivermead; e dois testes desenvolvidos para este estudo: o teste do relógio e o dos animais), bem como a testes cognitivos controles e Escala Cornell de Depressão em Demência. A análise dos dados usou o teste de Wilcoxon e o coeficiente de correlação de Spearman. **Resultados:** Os pacientes com DA foram inferiores aos controles nos testes de memória prospectiva e retrospectiva, em maior grau nesta última, sem que seu desempenho tenha se correlacionado com déficit de atenção, percepção ou função executiva. **Conclusão:** A memória prospectiva e, em maior grau, a memória retrospectiva estão primariamente e independentemente alteradas na DA leve.

PALAVRAS-CHAVE: memória prospectiva, doença de Alzheimer, demência, testes neuropsicológicos.

Memory complaints are usually the first and most important symptoms among Alzheimer's disease (AD) patients. Impaired ability to learn new information or to recall previously learned information (i.e., retrospective episodic memory) is required for the operational diagnosis of the disease¹. Memory is, however, a complex functional system and other types of memory (e.g., semantic, prospective) may be impaired early in AD. Episodic, semantic, and working memory are the most studied in AD. As conceived of by Tulving², episodic retrospective memory (RetM) represents events in our personal biographic his-

tory. It involves conscious recollection of these episodes (for example, when one was getting married), and it is typically evaluated by means of learning a list of words or a series of figures. Semantic memory constitutes our conceptual knowledge, for example, knowing that one is married without taking into account the time and place (episode) of the marriage; and working memory (as proposed by Baddeley)³ refers to the temporary, short-term storage of verbal-phonological, spatial and sensory informations that are being processed in any of a range of cognitive tasks (for example, when interpreting, learning, or reason-

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ing). In AD, RetM deficit, particularly the free and delayed recall of series of words, sentences, or objects, occurs earlier than the medial temporal atrophy shown by magnetic resonance imaging, and it is considered the most reliable predictor of the disease in its preclinical stage⁴. Impairment of prospective memory (ProM), though a common complaint of AD patients, has been neglected in cognitive studies of the disease. While RetM is the memory of the past, ProM is the memory of the future. ProM consists in remembering to carry out intended actions at an appropriate point in the future, such as to give your housemate the message that a friend called, keep appointments, pay bills, take medicine, and carry out domestic chores, so it is crucial for an older person to function independently in an everyday life context⁵. To perform a ProM task, one must remember there was an intention (the prospective component) and also to remember the contents of the intention, "what to do" (the retrospective component)⁶. ProM tasks can be either time-based (to make an intended action at a particular time of day or after a certain period of time has elapsed), event-based (to execute the intended action upon the occurrence of a particular environmental event), or activity-based (to do something when a particular activity has been completed)^{5,7}.

Several studies⁸⁻¹⁰ have shown that ProM is the memory type that most declines with aging, particularly when the prospective action is cued only by the time at which it has to be performed. Differential effects of aging on memory are more remarkable when the elderly has to rely on internal, self-initiated reminding, and less when there are more environmental, external cues, so that age differences are large in prospective tasks ("remembering to remember") and in free recall, and less in cued recall, and less again in recognition memory⁸. Other studies have provided evidence that ProM is sensitive to both aging and early onset AD, and that ProM impairment could be an indicator of the disease in its very earliest detectable forms, particularly when associated with apolipoprotein E ϵ 4 allele¹¹⁻¹³.

The main purpose of our study is to compare the performance of prospective and retrospective memory in patients with mild AD and matched normal controls. Since ProM seems to be the most vulnerable to the aging process, we hypothesize it would be more impaired than RetM in these AD patients.

METHOD

We studied 40 subjects, comprising 20 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 20 normal controls. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, serology for syphilis, thyroid hormones) and brain computed tomography were carried out in all patients.

This study was approved by our Medical School Ethics Committee and all subjects signed the informed consent form.

The diagnosis of probable mild AD was based on DSM-IV¹ and NINCDS-ADRDA criteria¹⁴. We included only patients with scores between 16 and 24 on Mini-Mental State Examination (MMSE)^{15,16} and score 1 on Clinical Dementia Rating (CDR)¹⁷. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs until 24 hours before the neuropsychological assessment, drug or alcohol addiction and prior exposition to neurotoxic substances. The control group consisted of subjects matched to the patients for age (± 5 years) and education (± 2 years), with CDR 0, and without previous history of neurological or psychiatric disease, or memory complaints. All patients were submitted to a detailed interview (even with the caregiver), the MMSE, and neuropsychological tests.

Neuropsychological evaluation comprised following tests

1) Retrospective episodic memory was examined with Rey auditory verbal learning test (RAVLT)¹⁸, which consists of fifteen words read aloud for five consecutive trials (list A), followed by a free-recall test. After the fifth trial, a new interference list of fifteen words is presented (list B) followed by a free-recall of that list. Soon afterwards, a free-recall of the first list is tested without new presentation. After a twenty-minute delay period, subjects are again required to recall words from list A. Finally, the patient must identify list A words from a list of fifty words which includes lists A and B and twenty other words phonemically or semantically related to lists A and B.

2) Prospective memory was evaluated with two subtests of the Rivermead Behavioral Memory Test (RBMT: the appointment and the belonging test; after Wilson, Cockburn and Baddeley)¹⁹; and two tests developed by the authors: the animals and the clock test. The ProM total score varied from 0 to 10.

2.1) Remembering an appointment: the subjects are required to ask for their next appointment when they hear the ringing of the alarm clock, which is set to go off 15 minutes after the instruction is given. Scoring system: 1 point if the correct response was made following a prompt ("What were you going to do when the alarm rang?") and 2 points if it was made without a prompt (maximum score=2).

2.2) Remembering a belonging: at the beginning of the session, the examiner borrows from the subject a personal belonging (pen, comb), which the examiner hides at sight of the subject (e.g., into a drawer or cupboard) with an instruction that the subject ask for it to be returned at the end of the test session. Then, at the end of the session, the examiner says "That is the end of the testing session". If the subject does not spontaneously request the belonging the examiner gives a prompt: "Was there something you were going to ask me for?" Scoring: 1 point if the subject recalled the item, another if he recalled the location and additional points for each response which was made without a prompt (maximum score=4).

2.3) Animals' test: subjects are told that they are going to see 20 photographs of animals on the computer screen, one at a time (during five seconds), and that his (her) task is to name each animal (naming task) and, in case he (she) sees some object or food in the mouth of the animal, to inform this to the examiner (this is the ProM task, embedded in the naming task). For the ProM task there are two photographs: one in the fifth and another in the tenth position. Scoring: 1 point for each correct ProM response (maximum=2 points).

2.4) Clock test: at the beginning of the session, the subject is asked to remind the examiner of an appointment five minutes afterwards, with the instruction: "In five minutes I have to tell to the nurse about a medication. Could you please remind me to tell to her when five minutes has passed?" This time is occupied with other tests or activities. There must be a clock visible in the periphery of the subject visual field. Scoring: 2 points if the subject reminds the examiner after five minutes with an error of (\pm) 30 seconds; 1 point for errors higher than this (and 0 point if no reminding); (maximum score=2).

3) Control tests (counterproofs) comprised: (a) visual perception (10 abstract figures modified from Jones-Gotman et al.)²⁰; (b) attention: the forward and backward digit span subtest of WAIS-R²¹; (c) executive function: Trail Making A and B²²; and (d) Cornell Scale for Depression in Dementia (CSDD; Brazilian version adapted by Carthery-Goulart et al.)²³.

All subjects were asked to repeat the ProM instructions to ensure they had understood them. Before the execution of digit span, trail making, and animals' ProM tasks, the subjects underwent a short learning (training) trial.

Data analysis by means of Statistica software 6.0 used Student *t* test for intergroup (paired samples) comparisons of demographic data (age and educational level), Wilcoxon test to compare RetM and ProM scores, and Spearman coefficient for correlation between PM and counterproofs. Statistical significance considered was $p < 0.05$.

RESULTS

Demographic and neuropsychological data are presented in the Table. There were 9 men and 11 women in each group. Dementia patients had higher age (mean $75.6 \pm$ standard deviation 7.8 versus 74.1 ± 6.8 years; $t = 2.6252$, $p = 0.02$) but similar educational level as controls (5.6 ± 4.5 versus 5.8 ± 4.4 years; $p = 0.507$). They performed as well as controls on Digit Span forward ($p = 0.324$) and Trail Making A ($p = 1.00$), but worse on MMSE (22.6 ± 1.9 versus 29.0 ± 1.3 ; $p = 0.0001$), Digit Span backwards (3.3 ± 0.7 versus 4.0 ± 0.9 ; $p = 0.0005$), Trail Making B (12.3 ± 5.7 versus 21.0 ± 6.0 ; $p = 0.0001$), Visual Perception (8.1 ± 1.3 versus 9.0 ± 0.9 ; $p = 0.015$), RAVLT delayed recall (1.1 ± 1.6 versus 6.65 ± 2.6 ; $p < 0.0001$) and PM total scores (4.1 ± 2.5 versus 8.8 ± 1.2 ; $p < 0.0001$). Cornell Scale for Depression in Dementia (CSDD) showed no signs of depression in the de-

mentia group (which presented scores from 0 to 2) nor in the control group (scores from 0 to 1).

The comparison of dementia subjects as for their performance on PM (total scores) versus RAVLT-recall revealed they were worse on this last test ($p < 0.0001$; Wilcoxon test for paired samples). In this group, there were no statistically significant correlations (Spearman rank correlation coefficient, *rs*) between PM and RM performance ($p = 0.535$) nor between PM and neuropsychological control tests (visual perception, $rs = -0.069$; digit span forward, $rs = -0.095$; digit span backwards, $rs = -0.023$; trail making A, $rs = -0.225$; trail making B, $rs = 0.091$; and MMSE, $rs = -0.115$). In the control group there was no correlation between age and PM (Spearman $rs = -0.0187$, $p = 0.937$).

DISCUSSION

All subjects could understand what was expected of them in the tasks proposed. Even those who failed in ProM tests could at the end of the experiment remember the instructions which had been given to them. As regards our two ProM tasks (Animals and Clock tests), they were constructed with basis on McDaniel and Einstein⁵ guidelines for creating typically prospective and informative tasks: (1) not to be executed immediately after the intention, but delayed or postponed to some point in the future; (2) to be embedded in another ongoing activity; (3) to have constrained time window of opportunities for initiating the intended action; (4) to have limited time frame for accomplishing the action; (5) to be based on an consciously formed intention or plan; and (6) the formed intention should not be maintained in working memory, in the focus of consciousness, but temporarily forgotten by performing other activities, otherwise it would constitute a vigilance task, not a PM task.

The inferior performance of dementia patients on ProM and other neuropsychological tasks cannot be accounted for by higher age, since their ages were not more than five years higher than those of their matched controls. Besides this age difference being small, the effect of age on cognitive performance is usually secondary to the effect of educational level²⁴⁻²⁶, which was similar in our groups of patients and controls. Dementia patients failure on ProM tasks can neither be explained by deficit of attention, visual perception or executive function as there was no correlation between ProM and the control tests for these cognitive functions.

Contrary to our expectations based on Craik's²⁷ memory model, our mild AD patients performed worse on retrospective than on prospective memory tasks. This finding is, however, not surprising, since these patients were included insofar as they fulfilled DSM-IV criteria, which requires that all patients, by the start, must have impair-

Table. Demographic data and neuropsychological scores of patients with dementia (AD1 to AD20) and normal controls (CO1 to CO20).

Subjects	Age (years)	Education (years)	RAVLT recall	PM total	Visual perception	DSB	TM-B	MMSE
AD1	74	4	0	5	5	3	5	17
AD2	78	1	0	7	8	3	10	22
AD3	81	2	3	2	8	3	8	22
AD4	92	4	0	7	8	3	24	24
AD5	82	4	0	0	8	3	16	24
AD6	56	4	4	9	8	4	24	24
AD7	80	5	0	3	7	4	8	22
AD8	60	16	0	1	7	2	10	23
AD9	75	1	0	3	7	3	7	20
AD10	68	4	0	6	6	3	12	19
AD11	78	4	1	1	8	3	13	24
AD12	76	4	0	3	10	5	16	24
AD13	73	3	0	1	8	4	15	24
AD14	79	15	0	2	9	4	11	24
AD15	76	15	1	0	9	4	17	23
AD16	79	4	1	1	10	3	8	23
AD17	69	3	5	6	10	3	19	24
AD18	80	8	0	1	7	3	5	23
AD19	79	8	3	6	9	3	9	24
AD20	77	4	4	3	9	3	8	22
CO1	70	4	8	9	8	4	22	30
CO2	77	2	3	9	9	4	23	30
CO3	77	4	2	10	7	3	1	29
CO4	88	5	4	7	9	4	20	25
CO5	78	4	8	9	10	5	24	29
CO6	57	4	8	9	8	5	24	30
CO7	77	4	7	7	9	4	8	30
CO8	60	12	10	8	8	3	23	29
CO9	74	2	6	6	9	4	24	28
CO10	68	4	5	8	9	4	18	30
CO11	81	4	7	10	8	5	24	29
CO12	74	4	9	10	10	6	24	30
CO13	77	4	6	9	10	4	24	27
CO14	75	18	8	10	10	5	24	30
CO15	71	16	13	10	10	4	24	29
CO16	75	4	6	10	10	4	24	28
CO17	70	4	9	7	8	3	20	30
CO18	80	8	3	6	10	3	24	29
CO19	76	6	5	8	9	3	22	29
CO20	78	4	6	9	9	3	22	28

DSB, digit span backwards; TM-B, trail making B; RAVLT, Rey auditory-verbal learning test; PM, prospective memory; MMSE, mini-mental state examination.

ment of episodic hippocampal RetM, but not necessarily of ProM. There are indications that ProM and RetM depend on different cognitive processes and different brain regions²⁸. As we found in our study, ProM does not need to correlate to RetM. ProM performance is more reliant on intention formation, strategic planning, self-initiated retrieval, and interruption or inhibition of ongoing actions, which are cognitive processes highly dependent on the frontal lobes but not on the hippocampal system²⁹. In

fact, positron emission tomography (PET) studies of young adults performing ProM tasks have found several localized brain activations, particularly in the right dorsolateral and ventrolateral prefrontal cortices, anterior cingulate gyrus, left parahippocampal gyrus, and midline medial frontal lobe^{30,31}. The authors related these localized activations to specific cognitive operations involved in ProM, such as holding an intention toward future behavior, checking target items within presented stimuli, and dividing atten-

tion between the planned ProM action and the routine activity in which it was embedded.

Although ProM was less deteriorated than RetM in our mild AD patients, it was markedly impaired in these patients as compared to normal controls, what suggests ProM may be an early indicator of dementia, as proposed by Huppert and Beardsall¹¹. In old subjects with preclinical AD or mild cognitive decline (with MMSE scores ranging from 18 to 30) both ProM and RetM are weakened, with the impairment of ProM affecting equally its prospective and retrospective components²⁸. Furthermore, most ProM studies of normal aging have observed differences between older subjects (in their 70s) and younger subjects (in their 50s), with the older ones performing worse³², although some studies have found no age-related differences in ProM³³, even in the context of age-related decline in RetM performance⁷⁹. As shown in Maylor's⁹ study, these discordant findings may be explained by the degree of environmental support (cues) and processing demands present in the different ProM tasks employed by the authors. Thus, in spite of these controversies, the bulk of evidence supports Craik's model in understanding the different effects of normal aging on ProM performance.

In conclusion, this study provides clear evidence that ProM and, in higher degree, RetM are primarily and independently impaired in mild AD. Some of its limitations should, however, be mentioned. First, all patients had full-blown dementia syndrome (though mild, with CDR 1), what makes it difficult to establish ProM as an early marker of AD. Second, the sample size is small and the scoring systems of ProM and RetM are different, what creates difficulties in running statistical analyses and in coming to safer conclusions. This study could be further improved by increasing sample size, including subjects in the preclinical phase of the disease, and using ProM tasks whose scoring systems tackle its prospective and retrospective components and facilitate comparisons with RetM tasks.

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