Memory complaints in amnestic Mild Cognitive Impairment: more prospective or retrospective?

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Abstract

Patients with amnestic Mild Cognitive Impairment (aMCI), usually considered an early stage of Alzheimer´s disease, have deficits not only in retrospective memory (RM), that is, recalling of past events, words or people, but also on prospective memory (PM), the cognitive ability of remembering to execute delayed intentions in the future. It is still controversial whether patients with aMCI refer more PM complaints as compared to RM complaints, and whether this might depend upon short-term vs. long-term items or time-based vs. event-based tasks.

Patients with aMCI (n=178) and healthy controls (n=160) underwent the Prospective and Retrospective Memory Questionnaire (PRMQ), a 16-itens instrument to appraise differences between PM and RM complaints, as well as a general mental state examination, a subjective memory complaints questionnaire, objective memory tests, and assessment of depressive symptoms and activities of daily living.

Patients with aMCI reported more memory complaints evaluated with the PRMQ (total score =44.3±10.8) as compared to controls (36.7±9.8, $p<0.001$). Using a mixed effect repeated-measures analysis of covariance (ANCOVA), showed that participants generally referred more retrospective than prospective memory complaints. Patients with aMCI had significantly more complaints on short-term memory as compared to long-term memory, and more complaints in time-based (auto-initiated) as compared to event-based tasks, than healthy controls.

In conclusion, patients with aMCI reported significantly more difficulties on short-term memory, presumably reflecting internal temporal lobe pathology typical of Alzheimer´s disease, and more complaints on time-based tasks, which are cognitively very demanding, but did not seem particularly troubled regarding prospective memory.

Keywords: prospective memory, retrospective memory, short term memory, long term memory, time-based, event-based, mild cognitive impairment

Introduction

Prospective memory (PM) is the cognitive ability of remembering to execute delayed intentions in the future, whereas retrospective memory (RM) refers to the recalling of past events, words or people[1]. Remembering to perform intended activities, like taking medication or attending an appointment, is indeed a fundamental requirement for independent living[2]. Prospective memory may be especially disrupted in Alzheimer's disease (AD)[3], presenting a severe threat to the individual's health and social relationships while increasing the burden of care[4,5]. Importantly, PM deficits may appear early in the neurodegenerative process, namely in patients that suffer from Mild Cognitive Impairment (MCI). Patients with MCI, and especially amnestic MCI (aMCI), are at high risk for developing full blown AD and usually considered an early stage of AD pathology[6]. Several studies showed that patients with MCI have objective deficits in PM, using different memory tasks[7,8,9,10,11,12]. Beyond the actual performance in PM objective tasks, it is also important to consider the subject's self-report about PM complaints. The Prospective and Retrospective Memory Questionnaire (PRMQ)[13] is probably the most widely used instrument to evaluate PM. This questionnaire also allows the comparison between PM and RM complaints. It contains 16 questions, split equally between items asking about retrospective and prospective memory symptoms. In addition, half of the prospective and half of the retrospective items refer to short-term and long-term memory problems, that is, memories remembered over brief periods of time or after longer delays. The PRMQ also considers whether or not external cues are available to elicit remembering of a previous event or action to be taken. The PRMQ instrument has been subjected to extensive validation in different populations and cultural backgrounds[14,15,16,17].

Several studies compared the frequency of prospective and retrospective memory complaints in MCI patients. In a study enrolling 77 patients with aMCI and 70 healthy controls, the PRMQ prospective subscale score and the PRMQ retrospective subscale score were similar in aMCI patients[18]. Another study recruited 27 patients with MCI and 71 healthy controls, as well as a few patients with mild AD. Again, the PRMQ prospective subscale score and the PRMQ retrospective subscale score did not differ in MCI patients, and were also not different in the healthy controls[4]. Ryu and colleagues studied 34 individuals with subjective cognitive impairment (SCI, corresponding to stage 2 on the Global Deterioration Scale[19]), 46 patients with aMCI and 35 patients with mild AD. Patients with aMCI, as well as patients with AD, had similar PRMQ prospective and retrospective subscale scores, however SCI participants presented more PM than RM complaints[20]. Another study compared self and informant-rated versions of the PRMQ in 48 patients with MCI (14

amnestic single-domain, 6 amnestic multi-domain and 28 nonamnestic cases), 53 healthy controls and 37 patients with dementia. Statistical analysis found no interaction between memory type, prospective or retrospective, and clinical group[21]. In contrast, another study enrolling 59 patients with Clinical Dementia Rating score (CDR) =0.5, that grossly correspond to MCI, and 21 participants with CDR=0, that is, healthy controls, as well as patients with CDR=1, that is, with mild dementia, found higher mean ratings for the PRMQ prospective subscale score as compared to the PRMQ retrospective subscale score. This effect was common for all the groups but led mostly by the CDR=0.5 group[22].

It is not known whether differences in the recruitment criteria, for instance based on MCI criteria *vs*. total CDR score, might contribute to the observed discrepancies regarding PM and RM involvement in aMCI. On the other hand, these studies enrolled a relatively small number of cases, and this might have contributed to inconsistency of the findings. It is also possible that patients with aMCI might have more specific prospective or retrospective memory difficulties, in relation to either short-term/ long-term memory items, or to time-based / event-based cues.

We now aim to clarify and detail whether patients with aMCI present differences in prospective and retrospective memory complaints, in comparison to healthy controls, and whether this might depend upon short-term *vs.* long-term items or time-based *vs.* event-based tasks.

Methods

Research Participants

Patients with aMCI were recruited at a dementia outpatient clinic and a memory clinic, both in Lisbon. The healthy control group were volunteers with no cognitive complaints from senior universities. The study was conducted in accordance with the Declaration of Helsinki and approved by local ethics committee. All participants were fully informed about the experimental protocol and gave their written consent.

Inclusion Criteria for the aMCI Group

Participants were diagnosed with amnesic Mild Cognitive Impairment (aMCI) when fulfilling the criteria of the amnestic MCI[23]:

(1) memory complaints

(2) abnormal memory function (immediate or delayed recall on the Logical Memory test of the Wechsler Memory Scale (story A) at least 1 SD below mean education and age values for the Portuguese population, this cut-off value was adopted considering that the use of the cut-off value of 1.5 SD could exclude subjects that from a clinical point of view suffered from aMCI[24]).

(3) normal general cognitive function (Mini Mental State Examination within normal values for Portuguese population)

(4) no or a minimal impairment in activities of daily living determined by the Instrumental Activities of Daily Living Scale (IADL; no more than one item from the IADL scale was altered)

Inclusion Criteria for the Control Health Group

(1) No memory complaints

(2) Normal memory function (values of immediate and delayed recall on the Logical Memory test of the Wechsler Memory Scale (story A) normal for the Portuguese population)

(3) No impairment on Mini Mental State Examination (MMSE) (normal values for the Portuguese population)

(4) Normal IADL scale (no item from the IADL scale was altered)

Inclusion Criteria for both groups

(1) Native Portuguese speakers

(2) Age > 45 years old

(3) Education level $\geq$ 4 years

Exclusion Criteria for both groups

(1) Dementia according to DSM-IV-TR[25]

(2) MMSE score below education-adjusted values for the Portuguese population

(3) Major depression according to DSM IV-TR or serious depressive symptoms (indicated by a score >10 points on the 15-item Geriatric Depression Scale - GDS_{15})

(4) Neurological disorders (Parkinson's disease, stroke, brain tumor, significant head trauma or epilepsy), psychiatric conditions (such as autism or schizophrenia), or uncontrolled medical illness (hypertension, metabolic, endocrine, toxic or infectious diseases) able to interfere with cognitive performance

(5) Psychoactive medications with possible influence on cognition

(6) History of alcohol or drug abuse

(7) Sensory deficits likely to interfere with assessment

Measures and Procedures

All the participants were submitted to the Portuguese versions of the following instruments:

(1) Mini-Mental State Examination (MMSE)[26,27]

(2) the normative cut-off values for the Portuguese population adjusted to education were used (abnormal performance is indicated by a score below 22 for subjects with ≤11 years of education and below 27 for subjects with >11 years of education)

(3) Logical Memory A[28] - This test evaluates verbal memory and is included in *Bateria de Lisboa para Avaliação das Demências* (BLAD)[29,30], a neuropsychological battery designed to evaluate multiple cognitive domains and validated for the Portuguese population. Participants with immediate or delayed recall on Logical Memory A below education and age adjusted values for the Portuguese population (1 SD) were considered to be impaired. A cut-off value of 1 SD was

adopted considering that the use of the cut-off value of 1.5 SD could exclude subjects that from a clinical point of view suffered from MCI[31,32].

(4) California Verbal Learning Test (CVLT)[33] – This is a test of verbal learning and memory. The trial of interest for the present study was the total number of words from List A correctly recalled on the five learning trials (A_1-A_5). The Portuguese version of the test was used[24]

(5) The Geriatric Depression Scale (GDS)[34]. The GDS is a questionnaire that evaluates the existence and the degree of depression. The 15-item version of the scale (GDS_{15}) was applied[35]. The maximum score is 15 and a score greater than 10 is considered to reflect serious depressive symptoms. The Portuguese version was used[36]

(6) Instrumental Activities of Daily Living Scale (IADL)[37]. The IADL is a tool that evaluates daily self-care activities. The Portuguese version, developed in the context of LADIS project, was used[38]

(7) Subjective Memory Complaints (SMC)[39] – The SMC is a self-report about own memory. The Portuguese version of the test was used[40,41]

(8) Prospective and Retrospective Memory Questionnaire (PRMQ)[13] – The PRMQ has 16 items, rated by frequency between 1 (never) and 5 (very often). Self-reported PM and RM complaints are equally divided, on eight questions each. PMRQ can also be equally subdivided by time-based or event-based tasks and by short-term memory or long-term memory. Higher scores mean more memory complaints. The Portuguese version of the scale was used[42].

Statistical analysis

For statistical analysis, SPSS Statistics® for Windows, Version 21.0 (IBM Corp.®, Armonk, New York), was used. A probability value of <0.05 was assumed as statistically significant.

Demographic, clinical and neuropsychological data were compared between aMCI patients and healthy controls with independent samples Student's *t* test for interval data and the Pearson´s χ^2 test for nominal data.

Global analysis of PRMQ scores was performed with a mixed effect repeated-measures analysis of covariance (ANCOVA). Patients with aMCI vs healthy controls were used for between-subjects effects, while memory type (prospective, retrospective), memory term (short-term, long-term) and memory aid (time-based, event-based) were used as within-subjects effects. The analysis accounted for age and depression (GDS_{15} score) using this variable as covariates, since both have been shown to influence the total PRMQ score. Differences in individual PRMQ items and subscale scores between the two groups were analysed with the independent samples Student's *t* test (no correction for multiple comparisons was done).

Correlations between PRMQ and demographic or neuropsychological variables were analysed separately for aMCI patients and healthy controls with the Pearson's correlation coefficient.

Results

Demographic and neuropsychological characterization

Participants were 178 patients with aMCI and 160 healthy controls. No statistically significant differences in terms of gender, age or education were found between the two groups. Patients with aMCI had poorer performances in MMSE and memory tests, as well as more depressive symptoms and more subjective memory complaints (Table 1).

Table 1 - Demographic and neuropsychological characterization

Variables	***aMCI (n=178)***	***Controls (n=160)***	***p value***
Gender, female/male	121/57	109/51	= 0.54[a]
Age, mean (SD)	69.5 (8.3)	67.7 (9.7)	= 0.07[b]
Education, mean (SD)	10.8 (4.5)	9.9 (4.7)	=0.07[b]
Immediate Logical Memory, mean (SD)	7.9 (4.1)	14.2 (4.9)	<**0.001**[b]
Delayed Logical Memory, mean (SD)	7.0 (7.5)	14.3 (5.8)	<**0.001**[b]
CVLT, mean (SD)	33.9 (10.1)	47.4 (15.9)	<**0.001**[b]
MMSE, mean (SD)	26.8 (2.4)	28.8 (1.5)	<**0.001**[b]
GDS, mean (SD)	4.5 (3.2)	3.1 (2.8)	<**0.001**[b]
SMC, mean (SD)	9.6 (3.9)	5.6 (3.3)	<**0.001**[b]

Abbreviations: aMCI, amnestic mild cognitive impairment; SD, standard deviation; CVLT, California Verbal Learning Test, total number of words from List A correctly recalled on the five learning trials (A1-A5); MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; SMC, Subjective Memory Complaints; [a], Pearson's χ^2 test; [b], Independent Samples Student's t-test.

PRMQ

Patients with aMCI reported more memory complaints when evaluated with the PRMQ (total score =44.3±10.8, *n*=178) as compared to controls (36.7±9.8, *n*=160; repeated measures ANCOVA, F(1,330)=24.086, $p<0.001$, $\eta^2_p=0.069$). Complaints were significantly more pronounced in RM (20.5±6.0) as compared to PM items (20.1±5.8, repeated measures ANCOVA, F(1,330)=4.345, $p=0.038$, $\eta^2_p=0.013$), however, they were not different in short-term (20.8±6.0) as compared to long-term memory items (19.8±5.6, repeated measures ANCOVA, F(1,330)=0.571, $p=0.450$, $\eta^2_p=0.002$). Complaints were also more prominent in time-based (auto-initiated, 21.8±6.4) as compared to event-based items (18.9±5.2, repeated measures ANCOVA, F(1,330)=4.933, $p=0.027$, $\eta^2_p=0.015$).

Interestingly, no interaction was found between the diagnosis and prospective or retrospective memory (repeated measures ANCOVA, F(1,330)=1.719, $p=0.191$, $\eta^2_p=0.005$), that is, patients with aMCI did not find more difficulties in either prospective or retrospective memory items as compared to controls. On the other hand, a significant and positive interaction effect was found between the diagnosis and the memory term (repeated measures ANCOVA, F(1,330)=7.655, $p=0.006$, $\eta^2_p=0.023$), meaning that patients with aMCI had significantly more complaints on short-term memory than controls. A significant

interaction was also found between the diagnosis and the type of memory aid (repeated measures ANCOVA, F(1,330)=16.129, p<0.001, η^2_p=0.047), that is, patients with aMCI had significantly more complaints on time-based (auto-initiated) items than controls.

Analysis of PRMQ individual items shows that patients with aMCI had higher scores in all PRMQ individual items (Table 2).

Table 2 – PRMQ – total, subscales and individual items scores, in patients with aMCI and healthy controls

PRMQ	***aMCI (n= 178) mean (SD)***	***Controls (n=160) mean (SD)***	***p value (a)***
1-PM-ST - time-based	3.20 (0.94)	2.50 (0.89)	**<0.001**
2-RM-LT - event-based	2.35 (1.04)	1.97 (0.94)	**<0.001**
3-PM-ST - event-based	2.50 (1.04)	2.06 (0.93)	**<0.001**
4-RM-ST - time-based	3.19 (0.87)	2.50 (1.00)	**<0.001**
5-PM-LT - time-based	2.88 (1.08)	2.31 (0.95)	**<0.001**
6-RM-ST - event-based	2.42 (0.95)	2.18 (0.94)	**=0.024**
7-PM-LT - event-based	2.66 (1.00)	2.40 (0.92)	**=0.015**
8-RM-LT - time-based	3.03 (0.95)	2.36 (0.95)	**<0.001**
9-RM-LT - event-based	2.57 (0.93)	2.25 (0.83)	**<0.001**
10-PM-ST - event-based	2.85 (0.95)	2.47 (0.78)	**<0.001**
11-RM-ST - time-based	3.24 (0.94)	2.69 (0.85)	**<0.001**
12-PM-LT - event-based	2.42 (0.97)	2.11 (0.82)	**<0.001**
13-RM-ST - event-based	2.40 (0.98)	1.86 (0.82)	**<0.001**
14-PM-LT - time-based	2.43 (0.95)	2.19 (0.95)	**=0.022**
15-RM-LT - time-based	2.93 (1.02)	2.49 (0.98)	**<0.001**
16-PM-ST - time-based	2.76 (0.96)	2.28 (0.86)	**<0.001**
PM	21.8 (5.9)	18.3 (5.1)	**<0.001**
RM	22.4 (5.9)	18.4 (5.3)	**<0.001**
PRMQ - Total score	44.3 (10.8)	36.7 (9.8)	**<0.001**

Abbreviations: PRMQ, Prospective Retrospective Memory Questionnaire; aMCI, amnestic mild cognitive impairment; SD, standard deviation; PM, Prospective memory; RM, Retrospective memory; ST, Short term; LT, Long term; (a) Independent samples Student's t-tests.

Correlations between PRMQ and demographic or neuropsychological variables

Significant correlations were found between the PRMQ total score and age, both in aMCI patients (negative correlation, r=-0.20, p=0.009) and healthy controls (positive correlation, r=0.30, p<0.001), but not between PRMQ total score and years of education. The PRMQ total score was significantly and directly correlated with the score obtained in another self-report scale about memory, the SMC, both in aMCI patients (r=0.59, p<0.001) and healthy controls (r=0.63, p<0.001). The PRMQ total score was also significantly and positively correlated with depressive symptoms evaluated by the GDS_{15}, both in aMCI patients (r=0.46, p<0.001) and healthy controls (r=0.39, p<0.001). Regarding the correlations between PRMQ scores and objective cognitive tests, it was remarkable that negative correlations were found for immediate and delayed logical memory and CVLT and MMSE, but only in healthy controls, not in patients with aMCI.

Discussion

The main results of the present study are that patients with aMCI report more retrospective than prospective memory difficulties. As expected, memory complaints, as a whole, were more prominent in patients with aMCI than in healthy controls. Patients with aMCI had significantly more complaints on short-term memory as compared to long-term memory than healthy controls. Participants generally reported more complaints in time-based (auto-initiated) as compared to event-based tasks, and these difficulties were even more pronounced in patients with aMCI.

As mentioned in the Introduction, previous studies have usually shown that patients with MCI reported equivalent complaints in the PRMQ prospective and PRMQ retrospective subscales[4,21,18,20,22]. Furthermore, a strong association was found between PRMQ prospective and retrospective memory subscales[18]. The present study shows that patients with aMCI actually reported more difficulties in RM. This result may seem surprising since patients with MCI show important deficits in objective PM tests[43,44]. It could be that patients with aMCI had a disproportionate unawareness of their PM deficits, as could be suggested by the observation that self-reported PM complaints were not correlated with the informant report[21]. However, self-reported RM complaints were not correlated with the informant report either, and the absence of correlations was similarly found in healthy controls[21]. We tend to envisage that the balance between the reports of PM and RM difficulties would largely depend upon the pathology underlying the MCI syndrome. It should be noted that previous studies often did not characterize the subtype of MCI participants or included heterogeneous MCI subtypes[7]. Since prospective memory is closely related to executive functions, non-amnesic MCI patients might report more prominent PM complaints than patients with aMCI[45,46]. It is important to emphasize that the present results were observed in patients carefully selected for aMCI, thus probably to be in a prodromal stage of AD and to display major difficulties in recalling past events. In the study of Eschen and colleagues, taken globally, PRMQ retrospective subscale scores were higher than PRMQ prospective subscale scores, and this effect was mainly attributable to AD patients[4]. In the same line, a study comparing individuals with subjective cognitive impairment, aMCI and mild Alzheimer's disease, found that PM complaints were equivalent among groups, but aMCI patients had more RM complaints than participants with subjective cognitive impairment[20]. The same researchers found that the PRMQ retrospective subscale score was inversely associated with the activities of daily living, presumably reflecting a neurodegenerative disorder, whereas the PRMQ prospective

subscale score was predominantly associated with higher depressive symptoms[47].

Patients with aMCI reported significantly more complaints on short-term memory than controls. Short-term memory problems with relative preservation of long-term memory have also been described as being common in normal aging[48], and short term memory is the most affected in aMCI[49], reflecting the degeneration of internal temporal lobe structures affected in Alzheimer's disease[50,51]. Healthy controls reported more difficulties in time-based items than event-based ones, and more so patients with aMCI. Time-based tasks are considered to be cognitively more demanding than event-based because it is believed they are dependent on executive functions, requiring more self-initiation[52,53,54,55,56]. Some studies report time-based tasks to be more affected in early aMCI and that this could be a sensitive measure for detecting initial memory deficits[57,58].

It is widely known that subjective memory complaints have weak correlations with objective memory measures[57] and otherwise healthy individuals with memory complaints frequently perform normally in memory tests as CVLT[59,60]. In the present study, inverse correlations were found between PRMQ scores and objective memory tests in healthy controls, meaning that healthy subjects could appreciate adequately the quality of their memory resources, but no correlations were found for patients with aMCI, that is, they seemed rather unaware of their own memory performance. Accordingly, in a cohort of nondemented patients with cognitive complaints, converters, who had poorer objective memory performances at baseline, actually scored lower in several items of the Subjective Memory Complaints (SMC) scale as compared to non-converters[61]. The absence of correlation between PRMQ scores and objective memory tests in patients with aMCI would likely represent some degree of anosognosia regarding their own cognitive deficits[62,63].

An important topic, which was not possible to address within the cross-sectional design of the present study, is how PM complaints and RM complaint compare in predicting evolution to dementia. PM complaints have been considered to be more sensitive to differentiate early dementia from normal aging[64]. Several studies found no differences between PM and RM as predictors of dementia[45,65,44], whereas others found PM complaints more accurate as a predictor of progression to dementia[18]. These discrepancies can be explained by procedural or methodologic differences in the recruitment of participants, namely on a clinical or population-based setting, and as discussed above, by the criteria used to define MCI.

In conclusion, patients with aMCI reported significantly more complaints on short-term memory than controls, presumably reflecting AD pathology, and more complaints on time-based items, which are cognitively demanding and healthy controls also find particularly difficult. Prospective memory did not seem predominantly affected in patients with aMCI, as manifested in the reported memory complaints using the PRMQ instrument, but since objective prospective memory tests were not performed, we do not know whether this subjective impression is paralleled in prospective memory performance or not. It is important to understand the role of memory complaints and particularly the specific characteristics of these complaints for the diagnosis of MCI, and for this purpose the PRMQ questionnaire can help to establish the profile of memory complaints and contribute to early diagnosis.

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