Retrograde Amnesia for Episodic and Semantic Memories in Amnestic Mild Cognitive Impairment

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Abstract. Retrograde amnesia (RA), which includes loss of memory for past personal events (autobiographical RA) and for acquired knowledge (semantic RA), has been largely documented in patients with amnestic mild cognitive impairment (aMCI). However, previous studies have produced controversial results particularly concerning the temporal extent of memory impairment. Here we investigated whether, with the onset of hippocampal pathology, age of memory acquisition and retrieval frequency play different roles in modulating the progressive loss of semantic and episodic contents of retrograde memory respectively. For this purpose, aMCI patients and healthy controls were tested for the ability to recall semantic and autobiographical information related to famous public events as a function of both age of acquisition and retrieval frequency. In aMCI patients, we found that the impairment in recollecting past personal incidents was modulated by the combined action of memory age and retrieval frequency, because older and more frequently retrieved episodes are less susceptible to loss than more recent and less frequently retrieved ones. On the other side, we found that the loss of semantic information depended only on memory age, because the remoteness of the trace allows for better preservation of the memory. Our results provide evidence that the loss of the two components of retrograde memory is regulated by different mechanisms. This supports the view that diverse neural mechanisms are involved in episodic and semantic memory trace storage and retrieval, as postulated by the Multiple Trace Theory.

Keywords: Cortical reallocation theory, mild cognitive impairment, multiple trace theory, retrieval frequency, retrograde amnesia, temporal gradient

INTRODUCTION

Retrograde amnesia (RA) refers to the inability to recall information acquired before the onset of the disease responsible for the memory impairment, as opposed to inability to learn new information (anterograde amnesia). With regard to RA, the most common distinction adopted in the literature is that between the episodic and semantic aspects of remote memories. Episodic (or autobiographical) RA refers to loss of memory for personally experienced incidents that happened in a specific space and time of one’s own past and whose retrieval is subjectively experienced as a sort of mental reliving of the specific event. Conversely, semantic RA indicates the loss of acquired knowledge, such as that related to famous people or public events, which does not have a specific time or location of occurrence. In a neurobiological perspective, damage to the medial temporal lobe (MTL) areas, comprising the hippocampus and parahippocampal cortices, has been postulated as critical in producing RA. However, the specific contribution of these structures to the storage and retrieval of past memories is
still controversial. Two conflicting theories of memory consolidation have been proposed. The Cortical Reallocation Theory, also known as the Standard Consolidation Model (SCM) [1, 2], suggests time-limited involvement of the MTL structures in the storage and recovery of both episodic and semantic traces; hence, over time the consolidation process leads to the formation of a permanent memory stored in the neocortex that is capable of sustaining the memory trace and mediating its retrieval alone [1]. Accordingly, the SCM claims there is no distinction between episodic and semantic memory with respect to their neural underpinnings in so far as all memory traces are initially mediated by the hippocampus, and then by cortical areas that do not include the MTL. Therefore, lesions to the MTL structures should result in a temporally graded RA, following Ribot’s [3] law, which affects both episodic and semantic memories. In other words, memories will be spared as long as they have been consolidated into neocortical networks, while more recent, not yet consolidated hippocampal-dependent memory traces, will be lost [1, 4]. By contrast, the more recent Multiple Trace Theory (MTT) [5, 6] makes a distinction between episodic and semantic memories regarding the neural mechanisms involved in memory trace storage and retrieval. Specifically, once the memory trace has been consolidated only semantic information fixed in neocortical networks is recalled independently of the hippocampal formation. Conversely, autobiographical episodes remain strictly dependent on the cortical-hippocampal system throughout a person’s life because these structures are always necessary for subjectively experiencing and recollecting the past in vivid detail as a sort of mental reliving of specific episodes [5, 7]. Furthermore, according to the MTT, episodic memories that are always mediated by the hippocampus are continuously updated and re-encoded after each retrieval, leading to the formation of multiple memory traces dispersed over wide areas of the hippocampal-neocortical system. Older episodic memories, which have been retrieved and re-encoded more often, will be stronger and more widely distributed in this system than recent memories. In line with the above described distinction between the two types of memories, different predictions regarding the impact of MTL pathology on the ability to recall past semantic information and episodic memories have been postulated. Concerning the semantic component, lesions to the MTL should lead to a temporally-graded RA, similar to that predicted by the SCM, in which older, well-consolidated semantic information is spared as long as it can be supported solely by extra-hippocampal structures in the neocortex, whereas more recent, hippocampal-dependent memories are lost. Conversely, the temporal extent and severity of autobiographical RA depends on both the amount of hippocampal damage and the age of the memory. Specifically, in the case of mild hippocampal damage the MTT forecasts a graded RA in which newly acquired—and thus less frequently retrieved—traces should be particularly vulnerable relative to older memories, which are multiply represented, and thus should be able to withstand the loss of more hippocampal complex tissue [5]. On the other hand, severe hippocampal pathology should lead to a flat gradient for detailed episodic information that extends throughout life because all autobiographical memories are claimed to be permanently dependent on the hippocampal complex.

Amnestic mild cognitive impairment (aMCI), which is characterized by episodic memory complaints without significant impairment in global cognition, is widely considered to be the prodromal stage of Alzheimer’s disease (AD), with progression rates of approximately 12% per year [8]. Neuroanatomical changes associated with aMCI comprise region-specific volume loss especially concentrated in the MTL, particularly in the hippocampus and entorhinal cortex [9–11], which accounts for the memory impairment typical of this pathology.

Deficits in remote episodic memory, investigated with autobiographical memory tests such as the Autobiographical Memory Interview [12] and the Autobiographical Interview [13], have been largely documented in patients with aMCI and AD from the early stages of the disease [14–16] (for a review, also see [17]). However, conflicting results have been reported about the presence or absence of a Ribot-like temporal gradient, with some authors reporting a significant temporal-graded amnesia in AD and aMCI [14, 15, 18] and others reporting no differences in memory recall between remote and recent incidents [19–21]. Similarly, signs of semantic RA have been reported in samples of aMCI and AD patients using tests of famous public events [22–27] and tests of famous faces or famous names [28–32]. But also for this type of information mixed results regarding the temporal extent and gradient of RA have been reported [22–25]. From the above it is clear that, although interest in studying remote memory has grown exponentially over time, behavioral studies in aMCI and AD have produced ambiguous results
and disagreement about the specific pattern of RA in these patients remains.

Whether earlier studies have primarily focused on how RA declines as a function of the time periods considered, i.e., from the most remote to the most recent ones, only few studies [26, 27, 33] have tested the impact of retrieval frequency on the extent and severity of remote episodic and semantic amnesia, as postulated by the MTT, in neurodegenerative pathology. In the first work [26], the authors assessed the recall of famous public events in early AD patients using a novel approach that allows evaluating separately how memory accuracy changes as a function of the age of the event (remote versus recent events) and retrieval frequency (more frequently versus less frequently retrieved events). They found that in all three tasks administered (subjective memory rating task, dating accuracy task, and contextual memory task) both early AD patients and normal controls derived similar benefits from greater retrieval frequency in terms of better memory performance independently of the age of the public events they had to recall. Langlois et al. [27] also investigated semantic knowledge about public events in aMCI and AD patients. They contrasted enduring events (i.e., facts that were recalled many times after their occurrence) and transient events (i.e., facts that rapidly went out of the public eye after their occurrence) through a forced-choice test. Similar to Muller et al. [26], they found no clear evidence of a temporal gradient; conversely, they reported better performance for enduring, and thus more rehearsed, events compared to transient, and thus less rehearsed, ones. Both studies concluded that frequency of retrieval, rather than age of memory, affects the severity of retrograde amnesia in clinical and preclinical AD. In a recent study by our group [33], we combined the Autobiographical Memory Interview [12] with the novel procedure used by Muller and colleagues [26] to evaluate memory for autobiographical incidents as a function of their age of acquisition and retrieval frequency in a sample of early AD patients. Compared with the two studies cited above, our findings provide new evidence that a combined action of both the time course and the retrieval frequency would offer a more exhaustive explanation of the pattern of autobiographical memory loss than only one of these two factors. Indeed, although both AD and healthy controls took advantage of greater retrieval frequency (i.e., higher scores on episodes rated as more frequently retrieved), in the AD sample the extent of its beneficial effect on memory performance was temporally-graded and inversely related to the time course. In a perspective that is closer to the MTT, it was hypothesized that frequency of retrieval protects episodic traces against the early damage of AD, whereas age of acquisition modulates the amplitude of this beneficial effect as a function of the remoteness of the trace.

Here we attempted to expand and clarify previous findings. Specifically, as we hypothesized that the mixed results reported in the above cited studies [26, 27, 33] are probably due to the different components of retrograde memory under investigation, the main aim of this study was to test whether retrieval frequency and memory age play different roles according to the semantic or episodic components of the memory to recall. For this purpose, a sample of aMCI patients and matched healthy controls (HC) were submitted to an experimental investigation of both semantic and autobiographical memories related to past public events in order: i) to evaluate the specific pattern of episodic and semantic RA in patients with mild hippocampal damage across different time periods and different degrees of retrieval frequency; ii) to examine whether the contribution of these two factors (retrieval frequency and age of memory acquisition) changes according to the type of memory.

MATERIALS AND METHODS

Participants

A cohort of eighteen patients suffering from aMCI (10 females) took part in our study. Patients were all recruited from the Alzheimer’s disease unit of IRCCS Santa Lucia Foundation of Rome from January 2016 to March 2017. All were submitted to formal clinical, neuropsychological, behavioral, and functional evaluation and a computed tomography or magnetic resonance scan as part of the diagnostic process. The aMCI patients were all classified as “amnestic single domain” according to the most recent clinical criteria [34], as they reported: (a) subjective complaint of memory decline (reported by the subject and confirmed by an informant); (b) objective memory impairment (revealed by scores below age/education-adjusted norms on at least one of the standard tests of episodic memory administered); (c) no significant deficits on the tests of the neuropsychological battery investigating other cognitive domains; (d) normal general cognition, as indicated by scores on the Mini-Mental State Examination (MMSE) above the normality cut-off (>23.8); (e) normal daily-life...
activities (as confirmed by a total Clinical Dementia Rating score less than or equal to 0.5). Furthermore, patients did not fulfill the clinical criteria for the diagnosis of dementia and had no history of drug/alcohol abuse or any psychiatric or neurological disease.

A group of eighteen age- and education-matched healthy individuals (10 females) were also recruited to serve as HCs.

All participants in our study were native Italian speakers and had lived in Italy continuously since 1960. They gave their written informed consent to take part in the study in accordance with the Declaration of Helsinki. The protocol utilized in this study was approved by the Ethical and Scientific Committee of Santa Lucia Foundation.

**Procedure**

Participants were tested individually during one session that lasted approximately 1.5 h each. To investigate the ability to recall episodic and semantic memories related to past public events as a function of both their age of acquisition and retrieval frequency, a novel questionnaire was developed. A total of fifty famous events, derived from previous Italian tests on famous historical events [35, 36], were selected and equally distributed across five broad time periods covering a lifespan of 46 years: segment A (1966–1975), segment B (1976–1985), segment C (1986–1995), segment D (1996–2004), and segment E (2005–2012). The ten famous events selected for each time segment were presented to the participants on a sheet of white paper in non-chronological order. The procedure consisted of two independent parts: retrieval frequency judgment was the first task and event recall was the second. We decided to keep these two procedures separate and consecutive (participants were not informed that after frequency judgment they would have to recall the chosen events) to avoid that the retrieval frequency judgment could be confounded with the vividness of the memories recalled.

The retrieval frequency task started when the participants were given the list of events included in segment A. They were first required to carefully read all the events and then to give a subjective judgment about which of the ten famous events they had recalled most often since its occurrence. In order to avoid misinterpretations, we clearly explained to the participants that they should not make an accuracy judgment (i.e., which of the ten famous events they remembered most at the time) but rather they should judge which of the events in their opinion was recalled most often since its occurrence based on media exposure, personal interests, contextual and emotional factors, etc. We repeated this statement every time the participants had to make a frequency judgment. At this point, the event chosen was categorized as frequency “One” (F1), according to participants’ impression that it was the event they had repeated most over time. Then we asked the participants to choose a second event from the list, scored as frequency “Two” (F2), that in their opinion had been frequently retrieved over time, but not as often as the event rated F1. Finally, they were required to choose a third event (scored as frequency “Three” – F3) they had heard/talked/thought about for only a limited time compared to the event scored as F2. This procedure was repeated for each of the subsequent time segments, from segment B to segment E, resulting in a total of 15 events selected (3 per time segment) by each participant.

After the retrieval frequency judgment, participants were tested for their capability to remember the chosen events. In this part, the ability to recall both semantic information and autobiographical episodes related to the past public events chosen was assessed independently. In the semantic subtask, the participants were asked to provide a description of each public event they had chosen in as much detail as possible. Each event was assigned a score ranging from 0 to 3 points. Specifically, 3 points were assigned for a fully exhaustive and richly detailed description of the public event, including the correct location in space and time of occurrence; 2 points were assigned for a detailed description of the event that was not fully exhaustive in the amount or richness of details; 1 point was assigned for a general/brief description of the main event that was poor in detail; and 0 points were assigned for a wrong description of the main event or for failure to provide any answer. In the semantic task, the maximum total score obtainable for each time segment was 9 (score range = 0–3 points per public event).

In the autobiographical subtask, participants were required to retrieve the personal incident regarding the first time they had had news of each public event in as much detail as possible. When the memory was generic, participants were encouraged to provide details. Each recalled episode was scored on an episodic scale ranging from 0 to 3 points. In particular, 3 points were awarded for a clearly defined, rich, and vivid episode located in a specific temporal and spatial context; 2 points were given for a
specific personal episode lacking in amount or richness of details; 1 point was assigned when a vague personal memory was produced; 0 points were assigned in the absence of any episodic retrieval or in the case of speculation/supposition. The maximum total score for each time period was 9 (score range = 0–3 points per personal event).

Both the semantic and the autobiographical narratives were audio-recorded and later transcribed. In order to prevent scoring bias, semantic and episodic memories were analyzed and scored by two independent raters. The degree of concordance between the two scores, calculated using Cohen’s Kappa (K) [37], indicated satisfactory inter-rater agreement (semantic: \( k = 0.94 \); autobiographical: \( k = 0.90 \)). Disagreements were examined and discussed until a consensus was reached.

**Data analysis**

Statistical analysis was performed with the STATISTICA v.9 package for Windows (StatSoft, Inc., Tulsa, OK USA). To detect between-group differences in age and education, one-way analyses of variance (ANOVA) were run. The non-parametric Mann-Whitney \( U \) test was used to detect group differences in the MMSE scores. Differences in gender distribution were assessed using a chi-square test. Repeated measures ANOVAs, followed by Newman-Keuls post-hoc tests, were used to examine the group performance on the semantic and autobiographical memory subtasks.

**RESULTS**

**Group characteristics**

As shown in Table 1, one-way ANOVAs of mean age and education showed no significant group differences. Furthermore, the two groups did not differ for gender distribution. As expected, the analysis revealed a significant difference for the MMSE.

### Table 1
| Demographic and clinical characteristics of HC individuals and aMCI patients. Mean scores with standard deviations in parentheses. HC, healthy controls; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; Max, maximum; \( n \), number |
|-----------------|-----------------|-----------------|-----------------|
|                | HC \( (n = 18) \) | aMCI \( (n = 18) \) | \( p \)-value |
| Female / Male  | 10/8            | 10/8            | 0.403          |
| Age (y)        | 71.4 (7.8)      | 73.4 (6.3)      | F\( (1,34) = 0.72 \) | 0.161          |
| Education (y)  | 13.7 (3.2)      | 12.1 (3.7)      | F\( (1,34) = 2.05 \) | 0.002          |
| MMSE (max 30)  | 29.4 (0.61)     | 27.7 (1.9)      | U = 66.5       | 0.002          |

**Semantic memory subtest**

Performance scores obtained by aMCI patients and HCs on the semantic memory task as a function of time period and retrieval frequency are presented in Fig. 1. The ANOVA with Group (aMCI versus HC) as between factor, Time Period (segments A, B, C, D, and E), and Retrieval Frequency (F1, F2, F3) as within factors revealed a significant main effect of Group (F\( [1, 34] = 48.11, p < 0.001, \eta^2 = 0.59 \)) due to the higher scores obtained by HCs (mean 2.38 SD ± 0.75) compared to aMCI patients (mean 1.40 SD ± 0.74). A non-significant trend was observed for Time Period (F\( [4, 136] = 2.05, p = 0.091 \)), suggesting that the memory performances of the whole group became progressively less accurate passing from the most remote periods to the most recent ones (segment A: mean 2.04 SD ± 0.84; segment B: mean 1.92 SD ± 0.84; segment C: mean 1.84 SD ± 0.89; segment D: mean 1.86 SD ± 0.92; segment E: mean 1.80 SD ± 0.94). A main effect of Retrieval Frequency emerged (F\( [2, 68] = 19.37, p < 0.001, \eta^2 = 0.36 \)) because of the higher scores in F1 (mean 2.11 SD ± 0.80) compared to F2 (mean 1.88 SD ± 0.87) \( (p = 0.002) \) and F3 (mean 1.68 SD ± 0.94) \( (p < 0.001) \), and in F2 compared to F3 \( (p = 0.004) \). Furthermore, there was a significant interaction between Group and Time Period (F\( [4, 136] = 2.74, p = 0.03, \eta^2 = 0.07 \)). Post-hoc analysis revealed that HCs performed similarly across all time periods (segment A: mean 2.39 SD ± 0.79; segment B: mean 2.33 SD ± 0.82; segment C: mean 2.35 SD ± 0.80; segment D: mean 2.39 SD ± 0.68; segment E: mean 2.43 SD ± 0.66), whereas MCI accuracy declined progressively as a function of the time period, indicating the presence of a temporal gradient. Indeed, scores obtained in the most remote time period (segment A: mean 1.69 SD ± 0.75) were significantly higher than scores obtained in the subsequent periods C (mean 1.33 SD ± 0.64; \( p = 0.03 \)), D (mean 1.33 SD ± 0.82; \( p = 0.02 \)), and E (mean 1.17 SD ± 0.75; \( p < 0.001 \)), as well as scores obtained in the time period B (mean 1.50 SD ± 0.64) were
higher than that in time period E \((p = 0.05)\). No other interaction between the main factors approached significance (Group × Retrieval Frequency: \(F[2, 68] = 0.50, p = 0.61\); Time Period × Retrieval Frequency: \(F[8, 272] = 0.39, p = 0.92\); Group × Time Period × Frequency \(F[8, 272] = 0.21, p = 0.99\)), suggesting that the effect of retrieval frequency on the recall of public events was similar across time periods in patients and normal controls.

**Autobiographical memory subtest**

Performance scores obtained by aMCI and HC on the autobiographical memory task as a function of time period and retrieval frequency are presented in Fig. 2. The ANOVA with Group (aMCI versus HC) as between factor and Time Period (segments A, B, C, D, and E) and Retrieval Frequency (F1, F2 and F3) as within factors revealed a main effect of Group \((F[1, 34] = 39.41, p < 0.001, \eta_p^2 = 0.54)\) because of the better memory performance of participants in the HC group (mean 2 SD ± 0.88) than those in the aMCI group (mean 1.07 SD ± 1.06). The Time Period effect was also significant \((F[4, 136] = 12.88, p < 0.001, \eta_p^2 = 0.28)\). As revealed by the post-hoc analysis, the whole group had a significantly lower performance in the most recent time period E (mean 1.14 SD ± 1.06) compared to all the other ones: segment A (mean 1.86 SD ± 1.01) \((p < 0.001)\), segment B (mean 1.66 SD ± 1.02) \((p < 0.001)\), segment
C (mean 1.56 SD ± 1.05) (p < 0.001), and segment D (mean 1.47 SD ± 1.13) (p = 0.002); moreover, scores were higher in segment A than in segment C (p = 0.01), D (p = 0.001) and marginally compared to segment B (p = 0.05). There was a significant main effect of Retrieval Frequency (F[2, 68] = 7.15, p < 0.001, ηp² = 0.59) due to the better performance obtained on the autobiographical incidents rated as F1 (mean 1.98 SD ± 0.99) compared to F2 (mean 1.52 SD ± 1.02) and F3 (mean 1.11 SD ± 1.05), and on episodes rated as F2 compared to F3 (p < 0.001 in all comparisons). The Group × Time period interaction was significant (F[4, 136] = 2.59, p = 0.03, ηp² = 0.07). Post-hoc tests revealed that the memory performance of HCs was poorer in the time period E (mean 1.72 SD ± 0.98) compared to the period A (mean 2.17 SD ± 0.84) (p = 0.02) and B (mean 2.11 SD ± 0.72) (p = 0.04), and was comparable in all the other comparisons (segment C: mean 1.96 SD ± 0.91; segment D: mean 2.06 SD ± 0.90). On the other hand, scores obtained by the aMCI sample became progressively lower passing from more remote periods to more recent ones, suggesting the existence of a temporal gradient. Indeed, performance in segment A was significantly higher (mean 1.56 SD ± 1.08) than in segments B (mean 1.20 SD ± 1.09) (p = 0.02), C (mean 1.15 SD ± 1.04) (p = 0.02), D (mean 0.89 SD ± 1.04) (p < 0.001) and E (mean 0.56 SD ± 0.79) (p < 0.001), as well as performance in segments B, C, and D was higher compared to that of the segment E (p < 0.01 in all comparisons). The significant Group × Retrieval Frequency interaction (F[2, 68] = 7.15, p = 0.002, ηp² = 0.17) highlighted that although both HC and aMCI took advantage from highest retrieval frequency in terms of memory performance, the extent of this varied between groups. Specifically, in the HC group higher scores were associated with autobiographical episodes rated as F1 (mean 2.28 SD ± 0.79) compared to F2 (mean 1.99 SD ± 0.85) (p = 0.02) and F3 (mean 1.74 SD ± 0.92) (p < 0.001) and to episodes rated as F2 rather than those rated as F3 (p = 0.05). Similarly, aMCI patients’ performance in F1 (mean 1.68 SD ± 1.08) was higher than in F2 (mean 1.06 SD ± 0.96) and both were higher than in F3 (mean 0.48 SD ± 0.75) (p < 0.001 in all comparisons). Nevertheless, although the effect of retrieval frequency was similar across the two groups (F1 > F2 > F3), the loss of accuracy passing from F1 to F3 and from F2 to F3 was significantly more marked in aMCI patients than in the control group (F1 minus F2: p = 0.107; F1 minus F3: p < 0.001; F2 minus F3: p = 0.018). Finally, the Group × Time Period × Retrieval Frequency interaction was significant (F[8, 272] = 2.32, p = 0.020, ηp² = 0.06). The crucial post-hoc analysis revealed that in the HC group episodes rated as F1, F2 and F3 obtained similar scores across all time segments, with the only exception regarding the time period D, in which F1 was higher than F3 (p = 0.03). Conversely, in aMCI group the difference in memory performance between the three levels of retrieval frequency was evident in the most remote periods but disappeared in the more recent periods. Specifically, the recall of episodes rated as F1 and F2 was more accurate than that of episodes rated as F3 in time periods A (F1 > F3, p < 0.001; F2 > F3, p = 0.008), B (F1 > F3, p < 0.001; F2 > F3, p = 0.01) and C (F1 > F3, p < 0.001; F2 > F3, p < 0.001). In the time period D, scores were higher F1 than in F2 (p = 0.008) and F3 (p < 0.001) and were comparable between F2 and F3 (p = 0.64). In the time segment E, instead, comparable scores were obtained across the three different levels of retrieval frequency.

**DISCUSSION**

In our previous study [33], we found that both retrieval frequency and age of memory play a fundamental role in modulating the pattern of autobiographical RA in early AD patients. However, different results have been obtained in assessing the pattern of semantic RA in the same type of patients [26, 27], because only frequency of retrieval, and not age of memory, affected the severity and extension of RA.

In the light of these mixed results, here we wished to test the hypothesis that these different findings could be due to the different kinds of memory being assessed. Specifically, we speculated that in the case of early hippocampal/MTL damage, frequency of retrieval and memory age might have different roles in characterizing the loss of retrograde memory depending on whether semantic or episodic memory has to be recalled, respectively. For this purpose, we administered a novel questionnaire that allowed assessing both autobiographical and semantic knowledge about famous public events as a function of both memory age (remote versus recent events) and retrieval frequency (high, medium, and low frequency) to a sample of aMCI patients and HCs.

First, we found that aMCI patients performed significantly worse than normal controls overall in
recalling both semantic and autobiographical memories. This result is in line with previous studies which reported a widespread impairment of remote memory from the preclinical phase of dementia [14, 16, 24, 26, 27] and also with the neuroanatomical changes that in aMCI first affect the hippocampus and the parahippocampal regions in the MTL [9–11].

Regarding the recall of semantic contents about public events, we found that, compared to normal controls, patients’ memory performance was characterized by a temporal gradient, in which remote memories were better preserved than more recent ones. This data is consistent with the results of other studies reporting a temporal pattern of retrograde impairments in MCI patients in the recall of public events or the identification of famous names [23, 25, 29, 32]. We also found a significant effect of retrieval frequency, i.e., public events rated as most frequently retrieved were recalled better than those rated as less frequently retrieved, which did not differ between the two samples of participants. This evidence reinforces the recent findings of Muller et al. [26] and Langlois et al. [27] who both reported the beneficial effect of repetition on the retrieval of past public events that was not related to the time period in which they were acquired and that characterized similarly the performance of both patients and normal controls.

Regarding the recall of the autobiographical context in which public events were first heard, we found evidence of a significant Ribot-like temporal gradient in patients’ performance, with better preservation of remote memories than recent ones. Also, this finding of a temporal-graded impairment of autobiographical memory is consistent with the results of many previous studies in aMCI [14, 15, 18, 38]. In addition, we found that in both groups better performance was associated with frequently retrieved episodes, which resulted as better preserved and recalled than those less frequently retrieved. Interestingly and in line with our previous study, we observed that this protective effect of retrieval frequency on memory accuracy was particularly evident in patients rather than HCs and, mostly, that in the aMCI group it seemed to be unstable over time. Conversely, this effect appeared to be inversely related to the time course, i.e., it had its maximum effect in the most remote time periods. Indeed, in time segments A, B, and C, aMCI were able to recall the episodes rated as most frequently retrieved with accuracy comparable to that of HC. Conversely, as the time segment became more recent, the advance of higher retrieval frequency was less marked, until it disappeared in the most recent time segment, suggesting a temporally-graded benefit of retrieval frequency on memory quality.

Taken together, the results of our study—in which the two components of retrograde memory (i.e., episodic and semantic) were evaluated separately in the same sample of subjects and concerning the same type of material (i.e., famous public events)—provide evidence that the loss of past autobiographical incidents and semantic information is regulated by different mechanisms respectively. In contrast with the SCM, which considers episodic and semantic memories as roughly similar with respect to their neural underpinnings, our data support the view that diverse neural mechanisms are involved in episodic and semantic memory trace storage and retrieval, as postulated by the MTT. On one side, the dynamic interaction between retrieval frequency and memory age observed in the autobiographical memory task seems a salient feature of patients’ memory performance and particularly, it seems to have an essential role in characterizing the pattern of episodic remote memory loss at least in aMCI and early AD patients. In a perspective closer to the MTT [5, 6], we speculated that the hippocampal complex might be permanently involved in the recall of episodic personal memories, as reinforced by recent neuroimaging studies [39, 40], and that the progressive loss of this type of memory might be due to the combined action of both retrieval frequency and time course. Specifically, the former factor protects the episodic trace against hippocampal atrophy, as more frequently retrieved memories are reinforced by more and stronger hippocampal-neocortical traces and, thus, become less susceptible to disruption by brain damage compared to seldom recalled, less represented, memories. In addition, the age of memory should change the amplitude of this beneficial effect as a function of the remoteness of the trace. Indeed, the MTT postulates that older episodic memories are associated with a greater number of traces than more recent ones. In this way, newly acquired memories should be more vulnerable in the case of mild hippocampal damage than older memories, which are multiple and more strongly represented and would thus be able to withstand the loss of more hippocampal complex tissue. In the last time segment, the slightly marked difference in memory performance between the three retrieval frequencies (revealing a flat gradient) disclosed by the aMCI group is in line with both the SCM and MTT models and also with our previous results. Indeed, relative to recent memories, which are likely acquired after the onset
of the disease, a pronounced frequency gradient is unlikely to be detected because the hippocampal atrophy does not allow the full consolidation of new memory traces.

In contrast with what we found for autobiographical memory, our results suggest that frequency of retrieval was not a salient feature in modulating the pattern of semantic memory loss in MCI, because the positive relation between retrieval frequency and memory accuracy has a similar effect on the performance of both patients and controls. As opposed to past autobiographical memories, which are always dependent on and multiply represented in hippocampal-neocortical networks according to their frequency of rehearsal and memory age, remote semantic memory benefits from the hippocampal contribution only for a limited period after which it can be supported only by the neocortex. By virtue of this, it is reasonable that in the case of mild hippocampal damage the loss of semantic information about past public events does not rely on retrieval frequency. Conversely, its beneficial effect seems to reflect the normal improvement of rehearsal/repetition on memory accuracy demonstrated in normal subjects [41, 42] and individuals with MCI [32]. On the contrary, as a significant temporal gradient in patient-related memory decline was obtained, in which the oldest semantic information was better preserved than the most recent semantic information, we hypothesized that time period has a critical role in the severity and extension of semantic retrograde amnesia. This result is congruent with both the SCM and the MTT, which agree that older semantic memories survive hippocampal damage as long as they can be supported solely by extra-hippocampal structures in the neocortex.

In summary, our findings suggest that with the onset of hippocampal pathology, as in aMCI and early AD, the loss of autobiographical and semantic retrograde memory is regulated by different mechanisms respectively. On one side, impairments in the ability to recollect past personal episodes seem to be modulated by the combined action of both memory age and retrieval frequency, as in the case of mild hippocampal damage the more frequently retrieved episodes are less susceptible to loss than the less frequently retrieved ones. Moreover, this pattern of memory decline, in which episodes that have been less rehearsed over time are primarily affected, first involves personal incidents that are more recent and progressively spreads out to the oldest ones, probably depending on the amount of hippocampal damage.

On the other side, the loss of remote semantic memories seems to depend only on the age of acquisition of the memory trace itself, as the remoteness of the trace allows for better preservation of the memory.

**DISCLOSURE STATEMENT**

Authors’ disclosures available online (http://j-alz.com/manuscript-disclosures/17-0317r1).

**REFERENCES**


