Running title: Familiarity in MCI

Familiarity in Mild Cognitive Impairment as a function of patients' clinical outcome four years later

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Abstract

Objective. The current study addresses the nature of memory difficulties in amnestic Mild Cognitive Impairment (aMCI). Whereas recollection is consistently found to be impaired in aMCI, the results regarding familiarity are divergent. One potential factor that could explain this divergence in findings relates to heterogeneity of aMCI patients, so that only those aMCI patients who are to develop AD may present with impaired familiarity. The present study aimed at testing this hypothesis.

Methods. A group of 45 aMCI patients and a group of 26 healthy older adults performed a verbal recognition memory test with the Remember/Know paradigm to assess recollection and familiarity processes. All participants were followed for 4 years with clinical and neuropsychological testing. At the end of the follow-up, 22 aMCI patients progressed to AD and 23 aMCI patients remained stable. Initial memory performance was compared between the three groups.

Results. Whereas recollection was severely diminished in all aMCI patients, familiarity accuracy (and consequently global recognition accuracy) was found to be impaired only in aMCI patients who subsequently developed AD.

Conclusion. These findings suggest that the enrichment of aMCI population with predementia stages patients may modulate the likelihood to observe familiarity deficits, and impaired global recognition accuracy may accompany incipient Alzheimer's disease.

Keywords: Mild Cognitive Impairment, recollection, familiarity, Alzheimer's disease.

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Introduction

Amnestic Mild Cognitive Impairment (aMCI) designates the presence of progressive memory deficits in individuals who are not demented and who retain relatively normal activities of daily living [1]. Given that patients with aMCI are at high risk of developing Alzheimer's disease (AD) [2,3], this syndrome has attracted considerable interest as it can inform about the predementia stage of AD. In particular, clinicians need a finer characterisation of memory deficits in aMCI that would qualify as an early cognitive marker of Alzheimer's disease.

To this end, the most promising distinction concerns recollection and familiarity [4, for a review] which designate the processes that subserve recognition of past experience. Recollection is defined as the conscious retrieval of the event together with contextual details from the encoding episode. It allows a rich remembering of what happened, where and when, accompanied by the feeling of reliving mentally the past event. For instance, remembering that we went to a barbecue at Paul and Joan's place last Saturday night and that it was a warm night is a case of recollection. In contrast, familiarity is conceived as an acontextual sense of prior occurrence. It allows the rapid recognition of people, objects and places that we previously encountered, and is accompanied by a feeling of knowing. For example, when we see a face in the bus, we can have the strong feeling that we have met this person before even if we cannot tell when and where. Impaired recollection was consistently observed in aMCI patients. However, the studies failed to reach a consensus regarding the fate of familiarity, as there were almost as many reports of impaired familiarity in aMCI as reports of preserved familiarity [5,6]. Given that impaired recollection associated with preserved familiarity can be observed in several populations including healthy older adults [7] and frontotemporal dementia [8], it is important to determine whether familiarity is actually affected or not in the early course

of AD as this could be a deficit specific to AD. Theoretically, given that the earliest site of neurodegeneration in AD is the transentorhinal cortex [9] and considering the critical role of this region in familiarity [10], it is likely that impaired familiarity represents the initial memory dysfunction in the course of AD. Actually, it may be the only subtle memory deficit in the preclinical stage of AD [11]. Next, with the rapid progression of neurodegeneration in the hippocampus and retrosplenial hypometabolism and atrophy, recollection deficits should accompany, and even dominate over, familiarity deficits in aMCI due to AD [11].

One critical factor that could explain the divergence in findings regarding familiarity in previous work concerns heterogeneity of the MCI population. Given that only a portion of aMCI patients is actually harboring an Alzheimer pathology, the emergence of a familiarity deficit may depend on the degree of enrichment of the aMCI sample with prodromal AD patients. Currently, only indirect evidence suggest that familiarity may indeed be impaired particularly in those aMCI patients who have the highest likelihood to progress to Alzheimer's disease. In a meta-analysis, Koen and Yonelinas [5] observed an effect size close to zero in single-domain aMCI indicating no decrease in familiarity, but a marginally significant effect size in studies including both single-domain and multiple-domain aMCI. As multiple-domain aMCI patients demonstrate typically a higher rate of progression to AD [12], this may be taken as indirect support to the idea of familiarity deficits as early cognitive marker of AD. Moreover, Wolk et al. [13] found that familiarity scores in a group mixing aMCI patients and healthy controls correlated with the "AD cortical signature", a measure of decreased cortical thickness across frontal, parietal and temporal regions that is sensitive to early AD [14,15].

In order to test the hypothesis that impaired familiarity-based memory occurs only in aMCI patients who are in an early stage of AD, the current medium-term longitudinal study retrospectively analysed recollection and familiarity performance in aMCI patients as a

function of the clinical outcome at the end of a 4-year neurological and neuropsychological follow-up. In aMCI populations, follow-up assessments have long been the preferential way to reveal the aetiology behind the MCI symptomatology. Even though aMCI is a frequent precursor of AD, follow-up evaluations also reveal variable outcomes, including stability of symptoms, return to normal cognition, evidence of psychiatric conditions and progression to non-AD dementia [16,17]. In this study, aMCI patients performed an episodic memory task in which the contribution of recollection and familiarity was estimated by means of the Remember/Know paradigm [18,19]. Then, patients were followed with neurological exams and neuropsychological assessments for up to 4 years. At the end of the follow-up period, patients were classified as a function of whether they developed clinically probable AD or were still diagnosed as aMCI and their recollection and familiarity estimates were compared according to this clinical outcome. In line with the idea that alterations of familiarity should be characteristic of early AD [13], we hypothesized that familiarity should be impaired compared to controls only in those aMCI patients who developed AD in the subsequent years. In contrast, recollection should be impaired in all patients as this function is sensitive to several conditions that could be associated with mild cognitive impairment [20,21].

Methods

Participants

The initial patient group consisted of 47 participants (21 women) who met the Mayo Clinic criteria for amnestic MCI [2] at inclusion. During follow-up examinations, the patients were re-evaluated with a neuropsychological battery and a neurological assessment. In the course of the follow-up, one patient died one year after inclusion and one patient was eventually diagnosed with progressive supranuclear palsy, so the data from both patients were excluded from the current analyses (final data set n = 45). Twenty-two aMCI patients met the clinical

diagnosis of Alzheimer's disease [22] 6 to 42 months after inclusion (MCI-AD, mean time to conversion: 21.4 months ± 11.4), and 23 patients still presented with aMCI 4 years after inclusion (stable MCI).

A control group of 27 healthy elderly participants (18 women) also participated in the study. At inclusion, subjects in this group had no cognitive or psychiatric problems, were free of medication that could affect cognitive functioning, and reported being in good health. During follow-up, 1 participant demonstrated cognitive decline compatible with a degenerative process and was therefore excluded from the analyses.

All three groups performed several neuropsychological tests assessing short and long-term memory and executive functioning (Table 1) and biomarkers of neurodegeneration were obtained to further characterize MCI patients. Structural neuroimaging (3D T1-weigthed image) was performed in 19 MCI-AD patients, 18 stable MCI patients and 22 controls. Cerebral glucose metabolism was measured with FDG-PET in 22 MCI-AD patients, 23 stable MCI patients and 26 controls. Group comparisons with SPM (for details about image analysis methods, see [23]) indicated that, compared to controls, MCI-AD patients showed significant hypometabolism in the posterior cingulate, temporo-parietal and lateral temporal cortices. They also demonstrated atrophy in the hippocampus as well as in parietal, temporal and frontal regions. Stable MCI patients had poorer metabolism in the posterior cingulate cortex compared to controls and hippocampal atrophy. This pattern of cerebral changes is consistent with previous reports in MCI [24-26]. For some participants (19 MCI-AD, 17 stable MCI and 11 controls), the presence of at least one ε4 allele of APOE genotype was searched for via blood samples (Table 1). There was no difference in the proportion of carriers between MCI-AD and stable MCI patients, $\chi^2 = .11$, $p = .73$.

According to the Declaration of Helsinki, all participants gave their written consent to participate to the study, which was approved by the institutional ethics committee.

Materials and procedure

All participants were tested individually. The experimental episodic memory task was adapted from Souchay et al. (2007). In the study phase, participants were presented with 20 cue-target pairs of French words in the centre of a computer screen. The cue word was printed in lowercase letters next to the target word, which was printed in capital letters. The two words were weakly associated. Participants were instructed to try and remember the pairs because their memory for the second (target) word would later be tested by using the first word as a cue. The pairs were shown in random order and each remained on the screen for 5 seconds.

After a short delay filled with instructions, the cued recall phase began. The cues were presented in random order. The participants were asked to recall the target word that was associated with each cue during the study phase. They had next to give a feeling-of-knowing judgement, indicating whether they thought they would be able to recognise the target in a later forced-choice recognition test (data not analysed here).

Finally, a five-alternative forced-choice recognition phase was administered. Each of the 20 target words was presented with 4 semantically related distracter words. The participants had to indicate which word they had seen in the study phase. Moreover, for each response, they were asked to give a Remember/Know/Guess judgement. Participants were instructed that a Remember response corresponded to the recollection of specific information relative to the stimulus encoded at the study phase; that a Know response referred to recognition on the basis of familiarity without recollection; and that a Guess response could be used when they were unsure about their response.

Statistical analyses

Analyses of variance (ANOVAs) were used to assess between-group differences (Group: MCI-AD, stable MCI, controls) on neuropsychological measures and on episodic memory measures: proportion of correct cued recall, proportion of correct recognitions, proportions of Remember, Know and Guess responses to targets and distractors, and dual-process signal detection model estimates of recollection ([proportion of Remember responses to hits minus proportion of Remember responses to false recognitions]/[1 - proportion of Remember responses to false recognitions] [27]) and familiarity (d-prime based on the Independent Remember/Know procedure, where the familiarity score for hits and false recognitions is given by the proportion of Know responses/[1 – proportion of Remember responses] [28]).

An additional analysis assessed which memory scores (cued recall, recognition memory, recollection and familiarity estimates) best classify individuals as belonging to MCI-AD or stable MCI using a stepwise discriminant function analysis.

For all analyses, the statistical threshold was set at $p < .05$.

Results

The demographic and clinical characteristics at inclusion of the final three groups are presented in Table 1. The MCI-AD, stable MCI and control groups were matched in terms of age, education, vocabulary abilities (Mill Hill test [29]) and scores on the Geriatric Depression Scale [30]. The MCI-AD patients had a poorer score on the Mattis Dementia Rating Scale [31] than stable MCI patients, who themselves performed more poorly than controls, $F(2, 68) = 21.3$, $p < .001$. The comparison of neuropsychological scores across the three groups (Table 1) showed that MCI-AD patients were significantly impaired compared to stable MCI and controls, whose scores did not differ significantly, in working memory, executive functioning,

continuous recognition memory, and recent autobiographical memory (of note, for the latter, stable MCI nevertheless showed a medium-size difference with controls, d = 0.79). Both MCI groups were equally impaired in remote autobiographical memory. Awareness of memory problems was also affected in MCI-AD patients, as they underestimated their difficulties as compared to stable MCI patients and controls.

Scores for the episodic memory task for each group are presented in Table 2. The ANOVA comparing cued recall performance between the three groups showed a significant and large group effect, $F(2, 68) = 12.59$, $p < .001$, $\eta^2p = .27$. Post-hoc Tukey's HSD tests revealed differences between all three groups (ps < .05), indicating that cued recall performance was poorer in MCI-AD patients than in stable MCI patients (d = 0.87) and controls (d = 1.52), and that stable MCI patients had impaired performance compared to controls (d = 0.62).

The ANOVA on the proportions of correct recognition responses in the 5-alternative forced-choice test revealed a significant and large effect of group, $F(2, 68) = 14.83$, $p < .001$, $\eta^2p = .30$. Tukey's HSD tests showed that MCI-AD patients had poorer recognition performance than both stable MCI patients and controls (ps < .01, d = 1.10 and 1.64 respectively), whereas stable MCI patients showed a medium-size difference with controls (d = 0.51) that did not reach statistical significance (p = .15).

For Remember responses, the ANOVA on hits indicated a large effect of group, $F(2, 68) = 15.48$, $p < .001$, $\eta^2p = .31$. Both MCI-AD and stable MCI reported less Remember responses to targets than controls (ps < .01, d = 1.78 and d = 0.83 respectively), and MCI-AD classified targets as Remember less often than stable MCI (p = .08, medium effect size, d = 0.83). The ANOVA on false recollections did not reveal any significant effect ($F(2, 68) = 1.35$, $p = .26$, $\eta^2p = .03$). Notably, there were very few false recollections.

For Know responses, the ANOVA on hits yielded a medium-size non-significant group difference, $F(2, 68) = 2.51$, $p = .08$, $\eta^2p = .06$. Two-by-two effect size of group

comparisons suggested that both patients groups were comparable (d = 0.10) and provided slightly more Know responses to hits than controls (MCI-AD versus controls, d = 0.58 and stable MCI versus controls, d = 0.59). Also, there was a significant and medium effect of group on false recognitions accompanied by a Know judgment, $F(2, 68) = 3.50$, $p < .05$, $\eta^2p = .09$. Post-hoc tests pointed to an abnormal rate of false Know responses in MCI-AD ($p < .05$, MCI-AD versus controls, d = 0.88), whereas stable MCI showed a medium-size non-significant difference with controls ($p = .17$, d = 0.58).

For Guess responses, there was no group difference in the proportion of Guess response given to targets, $F(2, 68) = .40$, $p = .66$, $\eta^2p = .01$. In contrast, the ANOVA on Guess responses to distractors yielded a significant group difference, $F(2, 68) = 6.66$, $p < .01$, $\eta^2p = .16$. Post-hoc tests showed that MCI-AD patients produced more Guess responses to distractors than the other two groups (ps < .05, MCI-AD versus controls, d = 0.99; MCI-AD versus stable MCI, d = 0.72), which did not differ ($p = .57$, d = 0.27). This may indicate that Guess responses reflected more often total absence of memory in MCI-AD patients, whereas controls and stable MCI patients may have used Guess responses for unconfident answers.

The ANOVA on recollection estimates showed a large group effect, $F(2, 68) = 16.25$, $p < .001$, $\eta^2p = .32$. Recollection was impaired in both MCI groups, with a significantly larger deficit in MCI-AD patients than in stable MCI patients (Tukey's HSD tests, $p < .05$ for all comparisons; MCI-AD versus controls, d = 1.69; MCI-AD versus stable MCI, d = 0.80; stable MCI versus controls, d = 0.78). Finally, the ANOVA on familiarity estimates (d-prime) revealed a significant and medium effect of group, $F(2, 68) = 7.70$, $p < .05$, $\eta^2p = .12$. Post-hoc Tukey's tests indicated that only MCI-AD patients had significantly largely impaired familiarity accuracy ($p < .05$, MCI-AD versus controls, d = 0.85). In contrast, stable MCI patients' familiarity performance did not differ from that of controls ($p = .14$, d = 0.49). Of

note, both MCI subgroups did not differ ($p = .52$, $d = 0.42$), suggesting that stable MCI patients performed in-between MCI-AD patients and controls.

The results of the stepwise discriminant function analysis indicated that the best predictor of group membership was the recognition memory score, while the other scores did not significantly improve the model (Wilk's $\lambda = 0.77$, $p < .001$). Recognition memory scores correctly classified participants with 72% sensitivity, 69% specificity and 71% total accuracy. Figure 1 illustrates the distribution of recognition scores in the three groups.

Discussion

If a patient with aMCI consults at the memory clinic, can an investigation of recollection and familiarity help to refine his/her prognosis? Past research has unanimously reported impaired recollection, but has been divergent with regard to familiarity. In the current study, we tested the hypothesis that impaired familiarity should be seen especially in those aMCI patients who actually progress to Alzheimer's disease in the subsequent years. This prediction relies on the fact that initial neurodegeneration in the course of Alzheimer's disease affects the transentorhinal cortex, which is thought to support familiarity [11,13,32]. More precisely, when the symptomatic stage of MCI-due-to-AD is reached, patients should present with impaired familiarity associated with pathology in the transentorhinal cortex as well as severe recollection deficit due to the widespread pathology to regions underlying this function [11].

The main finding of the study was that aMCI patients who presented the clinical symptoms of Alzheimer's disease within 4 years of follow-up (i.e., MCI-AD) had impaired familiarity accuracy at baseline when compared to healthy older controls. The deficit emerged mainly as an increased rate of false recognitions based on familiarity, indicating a misleading reliance on familiarity rather than a reduction in the frequency of its use. In contrast, aMCI patients who were stable after 4 years showed small-to-medium-size non-significant decrease

of familiarity compared to controls. Moreover, both aMCI groups had severely impaired recollection, more so for aMCI patients who developed AD. The other measures of the task align with this pattern: cued recall (which is more similar to recollection than to familiarity) was much diminished in both aMCI groups, with the largest deficit in MCI-AD. Global forced-choice recognition scores were largely deficient in MCI-AD, as was also continuous verbal recognition memory in the additional test battery. Discriminant analysis showed that recognition memory was the best predictor of subsequent AD in MCI.

In dual-process models of recognition memory, accurate global recognition memory usually necessitates the efficient and independent contribution of both recollection and familiarity [4]. So, the severe impairment of recognition memory observed in MCI-AD is consistent with the fact that both recollection and familiarity were affected. In stable MCI patients, non-significant medium-size decline compared to controls suggested relatively better preserved global forced-choice recognition memory. The slight decline in stable MCI patients' performance may reflect reliance on familiarity to decide among alternatives that only partially compensate for impaired recollection [33,34]. Among the main memory scores (cued recall, recognition memory, recollection and familiarity estimates), recognition memory was the only significant predictor that allowed to classify whether a participant belongs to the MCI-AD or stable MCI group with 71% accuracy. This extends previous findings showing that a recognition memory score was a better predictor of MCI versus controls status than a recall score [35].

Here the fact that aMCI patients at baseline were in the prodromal stage of AD was determined via a neuropsychological and neurological follow-up. The emergence of clinical symptoms that are characteristic of typical AD [22] was the criterion for classifying the patients as being in the predementia stage at baseline. Currently, the dominant approach to determine whether aMCI is due to AD would be to collect biomarker-related information, such as CSF

or PET measures of amyloid and tau protein accumulation [36]. However, data collection for this study started before the advent of amyloid and tau biomarker-related research (2007-2008). Nevertheless, group comparisons of FDG-PET and grey matter density imaging data revealed brain changes in MCI-AD patients which have been typically attributed to MCI due to AD, thus comforting the clinical diagnosis [24-26].

Those aMCI patients who were still diagnosed as aMCI 4 years after inclusion formed most probably a very heterogeneous subgroup whose actual aetiology is not known. Among them, stability of diagnosis may indicate that they were still early in the course of AD and would develop dementia symptoms only later on, or may present with a slowly progressive form of AD. Alternatively, patients from the stable MCI group could return to normal if memory decline was due to transient affective or sleep difficulties [16,17,37]. Others may also harbour other types of neurological conditions (such as Parkinson's disease, supranuclear palsy, etc) or psychiatric conditions (e.g., major depression). For the current data, we consulted a posteriori the medical records of individuals from the stable MCI group for indication about long-term evolution. No information was available for 2 of them. For the remaining 21 patients, medical records mentioned the presence of cognitive decline with loss of autonomy, suggestive of dementia, in 9 patients. Two others suffered from stroke a few years after our study. Five patients still complained about their memory, but did not seem to develop dementia in recent records. Finally, 5 subjects appeared to live independently at home and did not consult for memory decline anymore. Although to be taken cautiously given the lack of rigorous procedure to assess cognitive status in long-term follow-ups, these medical information support the idea of heterogeneity in the aetiology of MCI at the time of our study for those individuals.

The current study has some limitations. First, sample size was small relative to cohort studies, so that replication with a larger sample size is needed. Second, the standardized

follow-up of the patients was limited to 4 years post-inclusion. This left uncertainty about the actual fate of individuals in the stable MCI group. Future work should include longer follow-up assessment of MCI patients, as this might inform about cognitive profiles leading to rapid progression to AD versus to slow decline. Second, since the data were collected, theoretical views about familiarity have evolved to better capture its complexity. In particular, it has been suggested that there are different forms of familiarity, that only some of them depends on the transentorhinal cortex and would be impaired early in the course of AD [11]. Future work may include longitudinal testing from the preclinical stage to the dementia stage in order to unravel the chronological unfolding of recollection and familiarity deficits.

In sum, the current medium-term longitudinal study showed that aMCI patients who subsequently progressed to Alzheimer's disease within 4 years of follow-up and who presented with hypometabolic and structural patterns typical of early Alzheimer's disease demonstrated impaired recollection and familiarity accuracy. Moreover, poor recognition memory best discriminated between MCI-AD and stable MCI patients. For the clinicians, these results suggest that observation of impaired recognition memory, or more specifically impaired familiarity in a test designed to assess this process, could be taken as an alerting signal that the patient might be in a prodromal phase of AD.

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Figure caption

Figure 1. Boxplot of recognition memory performance as a function of group