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Research report

# Fast, but not slow, familiarity is preserved in patients with amnestic mild cognitive impairment

Gabriel Besson [a,b,*], Mathieu Ceccaldi [b,c], Eve Tramoni [b,c], Olivier Felician [b,c], Mira Didic [b,c] and Emmanuel J. Barbeau [a]

[a] Centre de recherche Cerveau et Cognition, Université de Toulouse, CNRS CERCO UMR 5549, France
[b] Institut de Neurosciences des Systèmes, Inserm UMR1106, Aix-Marseille University, Marseille, France
[c] APHM, Service de Neurologie et Neuropsychologie, CHU La Timone, Marseille, France

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ABSTRACT

Recognition memory – affected early in the course of Alzheimer Disease (AD) – is supposed to rely on two processes: recollection (i.e., retrieval of details from the encoding episode) and familiarity (i.e., acontextual sense of prior exposure). Recollection has repeatedly been shown to be impaired in patients with amnestic Mild Cognitive Impairment (aMCI) – known to be at high risk for AD. However, studies that evaluated familiarity in these patients have reported conflicting results.

Here, we assessed familiarity in single-domain aMCI patients ($n = 19$) and healthy matched controls ($n = 22$). All participants underwent a classic yes/no recognition memory paradigm with confidence judgements, allowing an estimation of familiarity and recollection similar to the approach used in previous studies. In addition, they underwent a novel speeded recognition memory task, the Speed and Accuracy Boosting procedure, based on the idea that familiarity is fast and hence that fast answers rely on familiarity.

On the classic yes/no task, aMCI patients were found to have impaired performance, reaction times, recollection and familiarity. However, performance and reaction times of aMCI patients did not differ from that of controls in the speeded task. This is noteworthy since this task was comparatively difficult for control subjects.

This dissociation within familiarity suggests that a very basic component of declarative memory, probably at the interface between implicit and explicit memory, may be preserved, or possibly released, in patients with aMCI. It is suggested that early subprocesses (e.g., fluency based familiarity) could be preserved in aMCI patients, while delayed ones (e.g., conceptual fluency, post-retrieval monitoring, confidence assessment, or even access to awareness) may be impaired. These findings may provide support for recent suggestions that familiarity may result from the combination of a set of subprocesses, each with its specific temporal signature.



* *Corresponding author*. CNRS CERCO UMR 5549, Pavillon Baudot CHU Purpan, BP 25202, 31052 Toulouse Cedex, France.
E-mail address: besson@cerco.ups-tlse.fr (G. Besson).
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## 1. Introduction

Patients with amnestic mild cognitive impairment (aMCI) – defined as a progressive memory impairment in participants with normal activities of daily living – are at high risk for Alzheimer's Disease (Petersen et al., 2001). More than a decade of research has shown that these patients are typically impaired on all tasks of declarative memory (Cohen & Squire, 1980), whether episodic (Irish, Lawlor, Coen, & O'Mara, 2011; Irish, Lawlor, O'Mara, & Coen, 2011; Piolino et al., 2003; Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012; Tramoni et al., 2012), or semantic (Barbeau et al., 2012; Greene & Hodges, 1996; Joubert et al., 2008, 2010; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002). Moreover, tasks assessing recognition memory, usually considered to be much easier than other memory tasks (Mishkin, Suzuki, Gadian, & Vargha–Khadem, 1997), are also impaired in these patients (Barbeau et al., 2004, 2008; Bennett, Golob, Parker, & Starr, 2006).

Recognition memory is thought to rely on the contribution of two processes: recollection and familiarity (Yonelinas, 2002). Recollection is defined as the conscious retrieval of associations and context, while familiarity is an acontextual sense of prior exposure. Neurofibrillary tangles, one of the pathological hallmarks of Alzheimer's disease, typically appear in the medial temporal lobe, and, more specifically, in transentorhinal and entorhinal cortices first, before progressing to the hippocampus and, later, to other brain areas (Braak & Braak, 1991; Van Hoesen, Hyman, & Damasio, 1991). The transentorhinal cortex is part of the perirhinal cortex, a brain area considered to play a critical role in familiarity (Aggleton & Brown, 1999; Bowles et al., 2007). By contrast, the hippocampus is thought to be crucial for recollection (Bastin et al., 2004; Turriziani, 2004; Yonelinas, 2013). According to this line of thought, familiarity should be impaired very early in Alzheimer's disease (Didic et al., 2011).

However, while recollection has been consistently shown to be impaired in aMCIs patients (Algarabel et al., 2009, 2012; Ally, Gold, & Budson, 2009; Anderson et al., 2008; Belleville, Ménard, & Lepage, 2011; Embree, Budson, & Ally, 2012; Hudon, Belleville, & Gauthier, 2009; Serra et al., 2010; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013; Wolk, Signoff, & DeKosky, 2008), findings concerning familiarity have been contradictory. While some studies are in favour of an impairment of this process (Algarabel et al., 2009, 2012; Ally, Gold, et al., 2009; Embree et al., 2012; Wolk et al., 2008, 2011, 2013), others report preserved familiarity (Anderson et al., 2008; Belleville et al., 2011; Embree et al., 2012; Hudon et al., 2009; Serra et al., 2010; Westerberg et al., 2006, 2013). This situation is particularly confusing and therefore requires further studies (Genon et al., 2013), especially since, if familiarity is fully intact, memory support programs could rely on this preserved aspect of declarative memory.

Although there can be different reasons for these discordant results concerning familiarity, such as the heterogeneous nature of aMCI patients as a group, this problem could also be related to the method used to assess familiarity. Indeed, classical paradigms have been criticized because they rely on strong assumptions (Wixted, 2007; Wixted, Mickes, & Squire, 2010). Moreover, most of them (e.g., Remember-Know or Process-Dissociation procedures) are based on indirect measures of familiarity as they focus on the assessment of recollection (Paller, Voss, & Boehm, 2007). In order to obtain a pure and direct index of familiarity, some studies proposed the use of forced-choice paradigms with highly similar foils as distractors, a type of task which is considered to principally rely on familiarity (Algarabel et al., 2009, 2012; Westerberg et al., 2006, 2013). However, studies using this methodology also failed to show convergent results (Algarabel, Fuentes, & Escudero, 2013; Embree et al., 2012; Migo & Westerberg, 2013). There is therefore a crucial need to develop a new approach to assess familiarity reliably.

One critical property of recognition memory processes is speed (Brown & Aggleton, 2001). Familiarity is supposed to be a fast process, whereas recollection is thought to be slower because of the time needed to retrieve associated contextual information (Besson, Ceccaldi, Didic, & Barbeau, 2012; Juola, Fischler, Wood, & Atkinson, 1971; Mandler, 1980). This is supported by the idea that familiarity depends on a fast neocortical route while recollection depends on slower hippocampal activity (Barbeau et al., 2007; Mormann et al., 2008; Staresina, Fell, Do Lam, Axmacher, & Henson, 2012). ERPs studies that investigated the temporal course of familiarity and recollection in classical old/new paradigms are in line with these findings. In patients with aMCIs still, no clear preservation or impairment of the component traditionally associated with familiarity (i.e., the FN400) has emerged (Ally, McKeever, Waring, & Budson, 2009; Galli, Ragazzoni, & Viggiano, 2010; Hoppstädter et al., 2013; Olichney et al., 2008; Saavedra, Iglesias, & Olivares, 2012; Schefter et al., 2013; Wolk et al., 2013). As no behavioural study has attempted to adopt a temporal approach of familiarity and recollection in patients with aMCI, it is also unclear if differential behavioural patterns over time can be found in aMCI.

Recently, a new paradigm, the Speed and Accuracy Boosting procedure (SAB) has been developed in order to estimate the speed of the fastest reaction time during visual recognition memory (Barragan-Jason, Besson, Ceccaldi, & Barbeau, 2013; Besson et al., 2012). The main advantage of this method is that participants are forced to use their fastest strategy using a response deadline (i.e., making them provide their answer very rapidly, *before* a time-limit, set in this study at 700 msec). Barragan-Jason et al. (2013) demonstrated that this procedure significantly speeds up subjects reaction time compared to classic recognition memory tasks. This allows to compute a distribution of reaction times under time pressure and also to analyse the first moment at which participants are able to perform the task, an index called minimum reaction time (Fabre-Thorpe, 2011; Rousselet, Macé, & Fabre-Thorpe, 2003). Findings in healthy participants suggest that performance on the SAB strongly relies on familiarity, especially for the fastest responses (Besson et al., 2012), in line with the view that familiarity is fast and automatic, while recollection is slower and controlled.

The present study reports on a group of aMCI patients and a group of matched healthy controls who performed two experimental paradigms. In the first paradigm, we used a classic yes/no visual recognition memory task with

confidence responses that allows estimating familiarity and recollection following the Dual-Process Signal Detection model (Yonelinas, 1994; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). The aim of this paradigm was to replicate results from the literature, that showed an impairment of both performance and recollection in aMCI patients, and to assess familiarity in this population using a classical paradigm. In the second paradigm, familiarity was assessed using the SAB. Based on the hypothesis that the neuroanatomical locus of neurofibrillary tangles onset impairs familiarity before recollection (Didic et al., 2011), we expected aMCI patients to have impaired familiarity on both tasks.

## 2. Materials and methods

### 2.1. Participants

Nineteen patients [age: 70 (*Standard deviation*, SD = 8), 11 females, 0 left-handed] strictly meeting criteria for single-domain aMCI (Petersen et al., 2001) were included. All had a memory complaint, a performance of more than 1.5 SD below the mean of matched control participants on the delayed free recall of a verbal memory task (Van der Linden et al., 2004), intact activities of daily living and no impairment in other cognitive domains like language, visuo-spatial skills, or executive function as assessed using an extensive neuropsychological evaluation. Brain imaging, routine biological survey, psychiatric interview and physical examination had been conducted prior to the inclusion into the present study in order to exclude patients with a memory impairment subsequent to vascular disease, tumour, subdural hematoma, treatment, and concurrent diseases interfering with cognitive function. Other exclusion criteria were a history of systemic and/or neurological disease and a modified Hachinski ischemic score $\geq 2$ (Hachinski et al., 1975).

Twenty-two elderly matched controls [age: 70 (SD = 10), 14 females, 2 left-handed] with normal cognitive functions and no history of systemic, mental, and neurological disorder were also included. All participants had normal or corrected-to-normal vision.

### 2.2. Stimuli

Stimuli consisted of two different sets of photographs of objects ($n = 188$, in task 1; $n = 220$, in task 2) used in previous studies (Besson et al., 2012). Objects were cut-out from the background and subtended a visual angle of ~4.1 × 4.5° (SD = ~2.9 × 2.9). These objects were as varied as possible and belonged to different categories. In each block, half were biological and half were man-made. Stimuli were presented using E-Prime software (Psychology Software Tools Inc.).

### 2.3. Task 1: yes/no task with Receiver Operating Characteristic (ROC) procedure

The procedure (adapted from Yonelinas, 2001) consisted of two identical blocks of an explicit recognition memory task with confidence judgements allowing deriving a ROC curve (for a review, see Yonelinas & Parks, 2007). In the study phase of a block, participants were first presented with 15 items under a shallow encoding condition. Participants had to categorize objects as either biological or manufactured by pressing "1" or "2" on a keyboard. Following this, participants were then presented with a second list of 30 items using a deep encoding "like/dislike" condition. The participants were asked to judge how pleasant they found the object using a 7-point scale. They were finally shown 15 new items using the same shallow encoding condition as previously described. "Buffer" items that were not included in subsequent analyses were presented before each encoding condition in order to train participants. Encoding was self-paced.

Because a pilot study has shown that this yes/no task was rather easy, the test phase began after 10–15 min of an interfering phase during which unrelated neuropsychological tests were administered. Before the onset of the test phase, participants were informed that all studied pictures, intermixed with new pictures (30 per block), would appear, and that each picture would appear only once. For each item, participants first had to respond "yes" or "no" depending on whether they recognized it or not (Fig. 1). Then, participants were asked to indicate their confidence response using a 6-point scale ("6": "certain old" to "1": "certain new"). They were instructed to be as accurate as possible in their responses, but also to spread out their answers among all six of the confidence intervals if possible (Yonelinas et al., 1998). The test phase started with four "buffer" items (two studied items to recognize among two items that were not studied), as an example of the procedure. The test phase was self-paced. All stimuli were presented one by one, in the centre of a grey screen.

### 2.4. Task 2: SAB procedure

The task consisted of three blocks of a recognition memory task and followed the same general structure as already used by our group in previous studies (Besson et al., 2012; Barragan-Jason et al., 2013). Each block began with a study phase, in which stimuli (30 targets) were presented one by one, in the centre of a grey screen. Participants were explicitly instructed to remember all single-trial stimuli. Each stimulus was presented at least 3 sec, before participants could press a button to move on to the next trial. The interfering phase consisted of the presentation of a cartoon during 3 min (colour cartoon from the Disney studios, played with sound on). The test phase ensued using the SAB during which participants had to recognize the stimuli that were presented earlier, intermixed with new stimuli (30 distractors) that they had never seen before.

Based on a classical go/no-go task, the SAB constrains participants to answer before a response deadline. Here, based on earlier findings (Besson et al., 2012), and because elderly participant are known to be slower than young participants, we used a response deadline of 700 msec. If a go-response was made before this response deadline, an audio-feedback was played, positive if the item was a target (hit), negative if the item was a distractor (false-alarm) (Fig. 1). If a no-go-response was made, an audio-feedback was given at the response deadline, positive if the item was a distractor (correct no-go), or

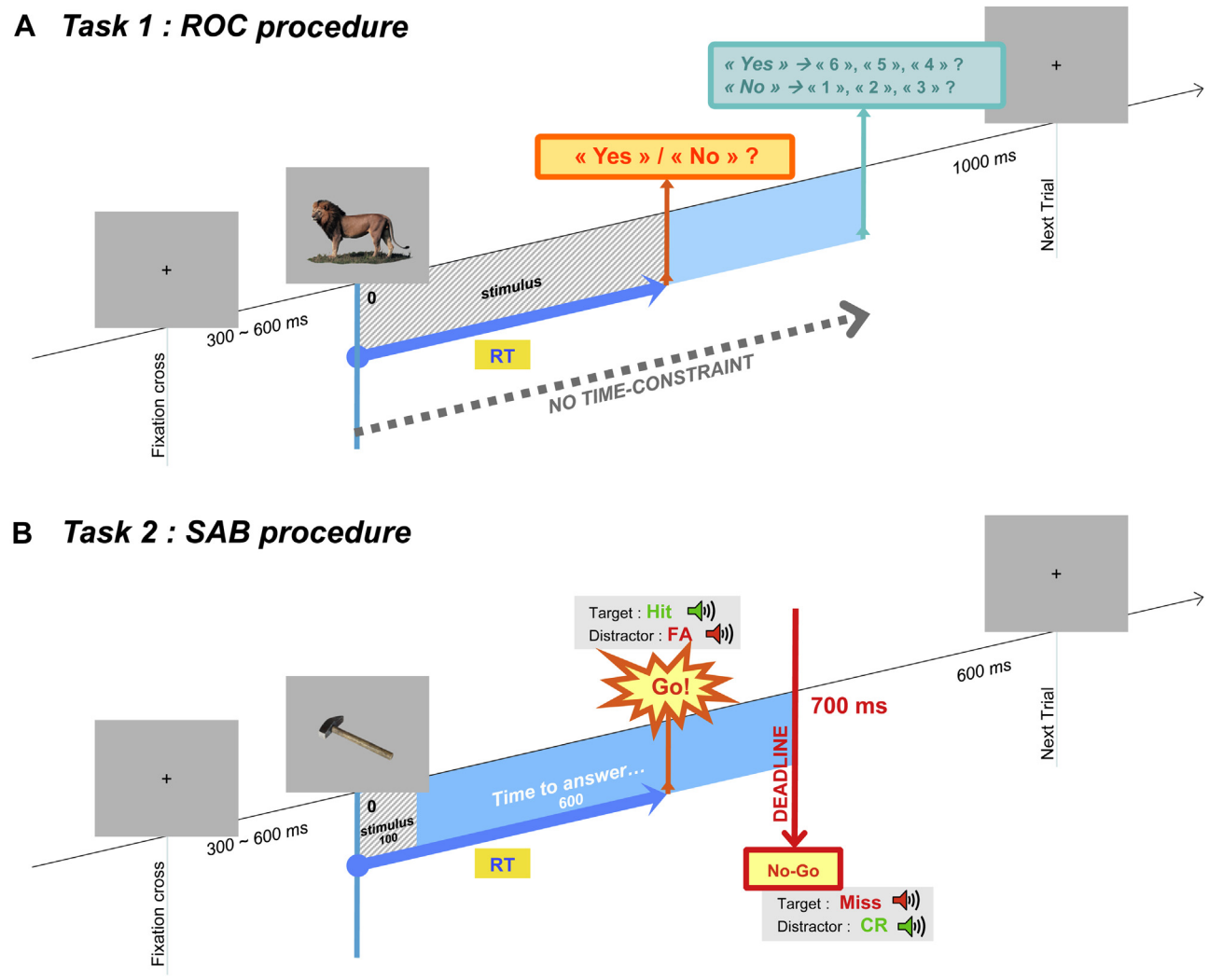


**Fig. 1 – Illustration of the test phases. (A) In task 1 (ROC procedure), participants first made a Yes/No judgement, before indicating their confidence-level. No time constraint was applied. (B) In task 2 (SAB procedure), participants had to make their go-response before 700 msec following stimulus onset. ***$p < .001$; **$p < .01$; *$p < .05$.**

negative if the item was a target (omission). The response deadline is presumed to boost speed and the audio feedback to boost accuracy. Before presentation of each item, a fixation cross was displayed for a random time between 300 and 600 msec. Items were presented for 100 msec (included in the response deadline). Because this is a highly demanding task, a self-paced pause was proposed every 20 items. The task was preceded by two training blocks (for each training block: 10 target stimuli, to be recognized among 10 distractors).

### 2.5. *Administration of the experimental paradigms*

Each participant (aMCIs and controls) underwent both experimental paradigms in the same session. The ROC paradigm was run before the SAB. Since the SAB constrains participants to respond as quickly as possible, running it first could have biased participants to respond faster during the ROC task. In contrast, letting participants respond spontaneously (i.e., rather slowly) during the ROC task, while constraining them to respond as fast as possible during the SAB, allows to maximize the contrast between both paradigms with the aim to compare slow and fast processes. The order of administration was not counterbalanced for this reason. Between these tasks, all participants underwent a verbal task that lasted for about 40 min.

### 2.6. *Familiarity and recollection index estimation from ROC curves*

Confidence-based ROC curves were generated for each participant and familiarity and recollection indexes were estimated using the Yonelinas High-Threshold model (Yonelinas, 1994; Yonelinas et al., 1998). Among the different model existing to describe recognition ROC curves (DeCarlo, 2003; Ratcliff, Sheu, & Gronlund, 1992; Rotello, Macmillan, & Reeder, 2004; Yonelinas & Parks, 2007), this model is widely

used to estimate familiarity and recollection, especially in patient populations (Ally, Gold, et al., 2009; Embree et al., 2012; Healy, Light, & Chung, 2005; Howard, Bessette-Symons, Zhang, & Hoyer, 2006). In particular, this model is the only one which relies on two parameters that provide directly quantitative estimates of recollection and familiarity. The method supplied by Yonelinas in a home-designed Microsoft Excel solver routine[1] was implemented in Matlab and computed for each participant to generate estimates of recollection (in percentage), familiarity (computed as a d′) and a residual index, an estimation of how well the model fitted the data.

### 2.7. Minimal reaction times

To obtain an estimation of the minimal processing time required to recognize targets, the minimal behavioural reaction time was computed by determining the latency at which correct go-responses (hits) started to significantly outnumber incorrect go-responses (false-alarms) (Rousselet et al., 2003). Analyses were performed either across trials (by pooling together all trials from all participants for a given task) and across participants. Across trials analyses have been used in previous studies (Barragan-Jason et al., 2013; Barragan-Jason, Lachat, & Barbeau, 2012; Besson et al., 2012; Rousselet et al., 2003) and are like building a "meta-participant", reflecting the performance over all the population. Minimal reaction times across trials were determined as the middle of the first bin that shows significantly more hits than false alarms ($\chi^2$-test, $p < .05$; followed by at least three significant consecutive bins in Task 2). Since reaction times were distributed differently between each paradigm, different time bins were used for each (30 msec in Task 1, 10 msec time bins in Task 2). Across participants, we used a Fisher's exact test ($p < .05$) in order to accommodate for the lower statistical power than across trials data. In order to accommodate for the very different distributions of RTs with and without speed constraints and keep comparable number of RTs within each time bin, we used 400 msec time bins in Task 1, and 40 msec time bins in Task 2. Within each task, identical time bins were used for participants. A minimal reaction time can't be computed if the distribution of hits does not reach a certain threshold above the distribution of false alarms. Thus, it was not possible to compute a minimal reaction time for some participants, in particular when d′ are low.

### 2.8. Statistical analyses

Statistical analyses were performed with Matlab and SPSS. Accuracy and bias were computed using d′ and C based on the signal detection theory (corrected according to Snodgrass & Corwin, 1988). Within each task, d′ and C measures were compared between groups using independent Student *t*-tests. Median reaction time (computed on Hits) verified the normality condition after a log-transformation. Mean and standard deviation reported for median reaction time were also computed after this transformation, and then replaced in the reaction time dimension by an inverse exponential transformation. Mann–Whitney tests were performed on minimal reaction time, familiarity index, recollection index and residual errors, as they globally did not verify normality assumption even after log-transformation. Hedges' *g* (an unbiased measure of Cohen's d) was used in order to compute effect size (Hedges & Olkin, 1985). Pearson's correlations were used to determine relationships between scores. In order to test for the effect of the task between groups on performance, each dependant variable (i.e., accuracy, bias, median reaction time) was analysed using a 2 (group: controls or aMCIs) by 2 (task: ROC from Task 1 *vs* SAB from Task 2) mixed factorial design with repeated-measures on the second factor. Simple effects were used to explore the effect of each factor. Significance threshold of *p*-value was set at .05.

## 3. Results

Demographical and clinical data are displayed in Table 1. Age, gender, and level of education were similar between groups.

### 3.1. Task 1: ROC procedure

Table 2 and Fig. 2 show the performance of aMCI patients and controls on the yes/no task.[2] In patients with aMCI, performance (d′, $t(39) = 3.10$, $p < .01$) and reaction time (median reaction time, $t(39) = -2.66$, $p < .05$) differed significantly from that of controls. A lower percentage of Hits ($t(39) = 2.86$, $p < .01$) and a higher percentage of FAs ($t(39) = -2.34$, $p < .05$) was also observed in aMCI, compared with controls. However, no significant difference in minimal reaction time [$U(18) = 225$, $p = .44$) or in bias ($t(39) = .32$, $p = .75$] was found. Moreover, aMCI patients were less accurate and slower than controls when providing high confidence answers (6-"sure old" and 1-"sure new") (Fig. 3).

Table 3 and Fig. 4 present estimates of familiarity and recollection. aMCI patients showed both impaired familiarity [$U(19) = 132$, $p < .05$] and impaired recollection [$U(19) = 120$, $p < .01$], while no statistical difference was observed between aMCIs and controls on residual errors [$U(19) = 228$, $p = .63$]. Effect size showed that recollection (*Hedge's* $g = .72$) was more impaired than familiarity ($g = .55$) in aMCI. No correlation was observed between recollection and familiarity, neither in aMCIs ($R^2 = .028$, $p = .50$), nor in controls ($R^2 = .13$, $p = .10$).

### 3.2. Task 2: SAB procedure

Neither accuracy[d′, $t(39) = .95$, $p = .35$], speed [median reaction time, $t(39) = 1.48$, $p = .15$], minimal reaction time [$U(17) = 174.5$, $p = .72$], bias [$t(39) = -.19$, $p = .85$], percentage of Hits [$t(39) = .89$, $p = .38$] or of FAs [$t(39) = -.71$, $p = .48$] differed between aMCI patients and controls (see Table 2 and Fig. 2).

[1] Available at http://psychology.ucdavis.edu/labs/Yonelinas.

[2] Shallow and deep conditions were pooled together because statistical power was low when these conditions were analysed separately. No interaction between groups and encoding conditions (deep/shallow) was found on accuracy, bias, RTs (median and minRTs) or recollection. There was, however, an interaction between group and familiarity [$F(1, 39) = 13.07$, $p < .01$], familiarity in controls being higher than in aMCI patients to a greater extent in the deep condition than in the shallow condition.

**Table 1 – Demographical and neuropsychological data for the two groups. All scores correspond to raw scores presented as mean [standard deviation (SD)]. MMSE = Mini-Mental State Examination; FCSRT = Free and Cued Selective Reminding Test (Van der Linden et al., 2004); FAB = Frontal Assessment Battery at bedside (Dubois, Slachevsky, Litvan, & Pillon, 2000).**

| | aMCIs | | Controls | | *p* |
|---|---|---|---|---|---|
| | *N* | 19 | *N* | 22 | |
| Demographical data | | | | | |
| Age-at-inclusion, in years | | 70 (8) | | 70 (10) | n.s. |
| Number of women, *n* (%) | | 11 (57.9%) | | 14 (63.6%) | n.s. |
| Level of education, in years | | 11.9 (3.4) | | 11.8 (3.4) | n.s. |
| Neuropsychological data (raw scores) | | | | | |
| MMSE (max = 30) | | 26.8 (1.5) | | 28.9 (1.4) | <.01 |
| Assessment of memory | | | | | |
| FCSRT – sum of free recall (max = 48) | | 16.8 (7.7) | | 28.3 (4.8) | <.001 |
| FCSRT – sum of free + cued recall (max = 48) | | 35.7 (8.6) | | 45.7 (2.1) | <.001 |
| Assessment of executive functions | | | | | |
| FAB (max = 18) | | 16.8 (.9) | | 17.0 (1.0) | n.s. |

Across trial analysis corroborated these results, showing a minimal reaction time of 410 msec for patients with aMCI compared with 440 msec for controls (Fig. 5). In particular, false alarms distributions were similar for both groups.

To assess whether performance changed across the three blocks, a two-way mixed design ANOVA with repeated measures with the block as a within-subject factor and the group as between-subject factor was carried out. This analysis did not reveal any main effect on accuracy [$F(2,39) = 2.218$, $p = .12$], on bias [$F(2,39) = 2.129$, $p = .13$] or on the percentage of hits [$F(2,39) = .0236$, $p = .98$]. A "near-threshold" main effect of block was observed on the percentage of FA [$F(2,39) = 3.115$, $p = .0499$].

### 3.3. *Comparison between the yes/no task and the SAB*

An effect of group [$F(1,39) = 4.974$, $p < .05$], an effect of the task [$F(1,39) = 100.4$, $p < .001$] and an interaction between group and task [$F(1,39) = 4.528$, $p = .04$] were observed on accuracy. Tests of simple main effects revealed that the SAB was more difficult than the yes/no task for both controls and aMCI patients ($p < .001$). However, within-participant differences between performance on the yes/no task and on the SAB were significantly smaller in aMCIs than in controls [$t(39) = 2.128$, $p < .05$].

A significant positive correlation of accuracy on the SAB with accuracy on the yes/no task was observed in controls ($R^2 = .28$, $p < .01$) and in aMCIs ($R^2 = .35$, $p < .01$). Furthermore, a correlation between the ROC estimate of familiarity and SAB accuracy was observed in aMCIs ($R^2 = .26$, $p < .05$), but not in controls ($R^2 = .10$, $p = .16$) while no correlation was observed between the ROC estimate of recollection and the SAB accuracy in either group.

## 4. Discussion

The aim of this study was to assess whether familiarity is impaired or not in patients with aMCI using two different

**Table 2 – Performance on both tasks. All scores correspond to raw scores presented as mean (SD). FAs = False alarms.**$p < .01$ between groups; *$p < .05$ between groups.**

| | | *Exp 1: ROC paradigm* | | *Exp 2: SAB procedure* | |
|---|---|---|---|---|---|
| | | Controls | aMCIs | Controls | aMCIs |
| Accuracy (d′) | Mean (SD)<br>range | 3.28 (.59)<br>[2.33; 4.21] | 2.57 (.87)**<br>[.99; 4.09] | 1.93 (.64)<br>[.80; 3.47] | 1.69 (.96)<br>[-.11; 3.04] |
| Bias (C) | Mean (SD)<br>range | .79 (.27)<br>[.16; 1.27] | .76 (.34)<br>[.07; 1.32] | .05 (.43)<br>[−.82; 1.34] | .07 (.46)<br>[−.55; 1.44] |
| Hits (%) | Mean (SD)<br>range | 91.9 (5.6)<br>[77.5; 100.0] | 83.3 (12.7)*<br>[49.2; 97.5] | 80.1 (12.5)<br>[44.4; 97.8] | 75.7 (19.5)<br>[16.7; 96.7] |
| FAs (%) | Mean (SD)<br>range | 4.2 (4.1)<br>[.0; 13.3] | 9.4 (9.5)<br>[.0; 35.0] | 18.6 (14.9)<br>[.0; 60.0] | 22.4 (19.3)<br>[1.1; 61.1] |
| Median reaction times | Mean (SD)<br>range | 1544 (480)<br>[860; 3419] | 2086 (868)*<br>[1153; 6595] | 536 (47)<br>[446; 651] | 502 (90)<br>[262; 606] |
| Obtained a minimal reaction time | *N* | 22/22 | 18/19 | 22/22 | 17/19 |
| Minimal reaction times | Median<br>1st and 3rd quartiles<br>range | 1200<br>[800; 1200]<br>[800; 2000] | 1200<br>[800; 1600]<br>[800; 3200] | 480<br>[440; 520]<br>[400; 600] | 480<br>[440; 490]<br>[320; 680] |

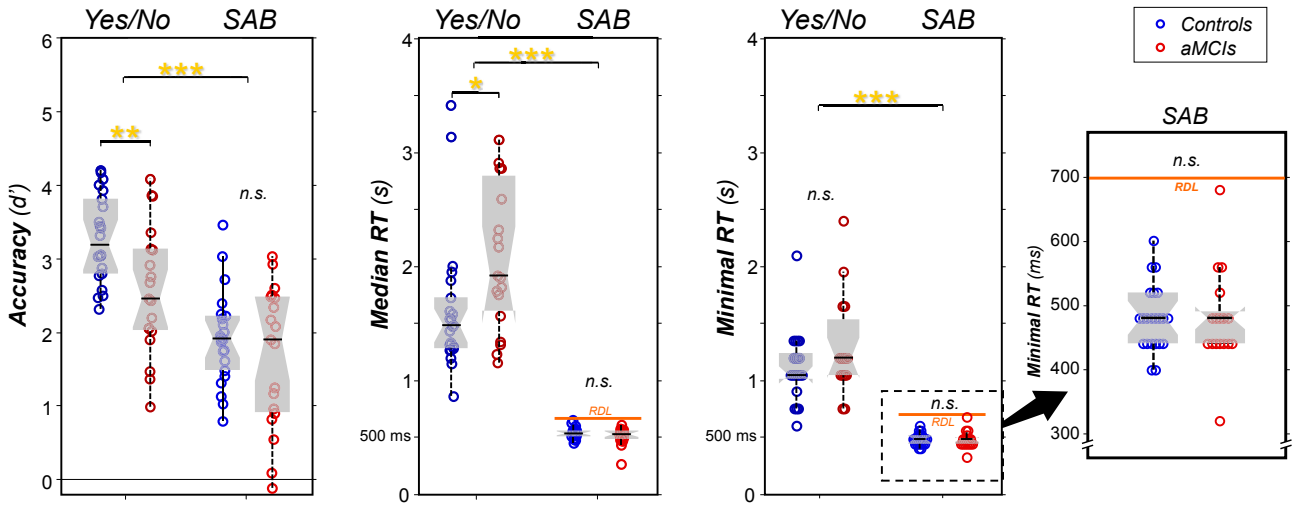


**Fig. 2 – Results on the yes/no and SAB tasks.**

experimental paradigms assessing recognition memory. Performance and recollection were impaired in aMCI patients using a classical yes/no task with confidence judgements allowing an estimation of familiarity and recollection from confidence-based ROC curves, replicating previous reports from the literature. In line with our hypothesis and a growing number of studies, familiarity was also impaired on this task (Algarabel et al., 2009, 2012; Ally, Gold, et al., 2009; Embree et al., 2012; Wolk et al., 2008, 2011, 2013). By contrast, performance on the SAB, a novel speeded go/no-go task in which subjects are obliged to use their fastest recognition strategy, was preserved concerning all studied features (accuracy, minimal reaction time and median reaction time).

Preserved performance in aMCI patients on a visual recognition memory task, clearly demonstrated by the distribution of reaction times on the SAB, is surprising since it differs from almost all studies that report impaired recognition memory in these patients (Algarabel et al., 2009; Algarabel

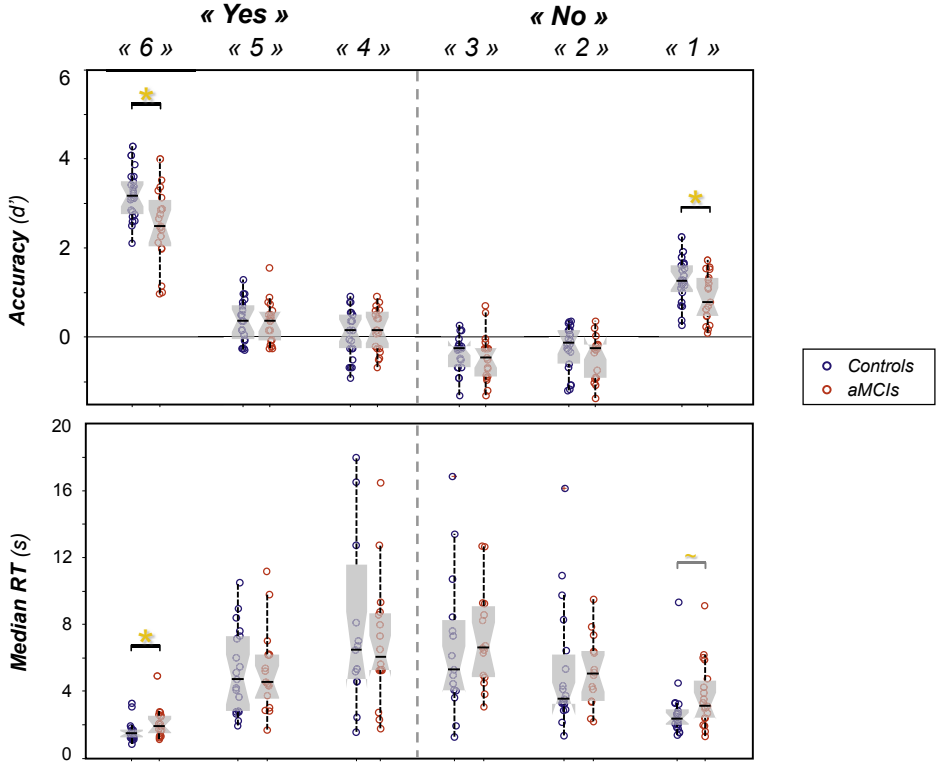


**Fig. 3 – d′ and median reaction time according to the confidence level in the two groups.**

**Table 3 – Estimation of familiarity and recollection indexes (based on the DPSD model) from ROC data of *task* 1.*$p < .05$ between groups; **$p < .01$ between groups.**

| | | Controls | aMCIs |
|---|---|---|---|
| Familiarity index (d′) | Median | 2.83 | 2.28* |
| | 1st and 3rd quartiles | [2.24; 3.26] | [1.39; 2.71] |
| | Range | [1.46; 7.79] | [.00; 6.03] |
| Recollection index (%) | Median | 60.9 | 24.3** |
| | 1st and 3rd quartiles | [26.4; 65.0] | [0; 54.0] |
| | Range | [0; 87.0] | [0; 89.9] |
| Residual error | Median | .03 | .03 |
| | 1st and 3rd quartiles | [.015; .047] | [.024; .045] |
| | Range | [>0; .088] | [>0; .13] |

et al., 2012; Ally, Gold, et al., 2009; Anderson et al., 2008; Barbeau et al., 2004; Barbeau et al., 2008; Belleville et al., 2011; Embree et al., 2012; Hudon et al., 2009; Serra et al., 2010; Wolk et al., 2008; Wolk et al., 2011; Wolk et al., 2013), especially as impaired recognition memory was equally found on the classic yes/no paradigm of the present study. Intact performance on the SAB is therefore even more intriguing considering that this was observed under challenging experimental conditions, as indicated by the significant strong decrease of performance between the two tasks in control subjects. This result clearly indicates that the SAB assesses different aspects of recognition memory than other tasks which all showed impaired performance in aMCI patients.

In line with the notion that the fastest responses in recognition memory are based on familiarity (Brown & Aggleton, 2001), a previous study in young healthy subjects indicated that performance on the SAB mainly relies on familiarity (Besson et al., 2012) (see Section 1). The fact that performance on the SAB was similar to that of controls in aMCI patients actually provides further support for this idea. Indeed, as recollection has consistently been shown to be impaired in patients with aMCI, a contribution of recollection to responses on the SAB would have impaired performance.

Because familiarity, as assessed by the SAB, was intact in the speeded condition, it would also have been expected to be preserved in the classic, unspeeded, yes/no paradigm, and even enhanced, due to information accumulation (Ratcliff, 1978). While an improvement of performance between the two tasks was indeed observed, a clear impairment of familiarity was however observed in the yes/no paradigm. Furthermore, and crucially, this improvement was significantly stronger in controls than in patients, implying that the temporal course of familiarity information accumulation is impaired in patients with aMCI. In addition, minimal RTs did not differ between groups, suggesting that the fastest processes underlying recognition memory in controls were preserved in aMCIs. Taken together, this may suggest that several processes contribute to familiarity over time, initial processes being preserved, the following being impaired.

Another intra-participant – and thus stronger – argument in favour of this interpretation is the observation of a significant correlation between the ROC estimate of familiarity and the SAB accuracy in the aMCI group, but interestingly not in the control group. Such a correlation would indeed be expected in aMCIs but not in controls if familiarity relies on fast and slow processes and if aMCIs show an impairment of slow processes but a preservation of fast ones.

This is in line with the recent idea that familiarity is complex and depends on the operation of several simple processes (Montaldi & Mayes, 2010). It has also been outlined that familiarity may have been oversimplified, by focussing almost exclusively on explicit expressions of memory while generally ignoring its implicit contributions (Voss, Lucas, & Paller, 2012; Voss & Paller, 2007). Hence, *perceptual fluency* (the fact that processing perceptual features for the second time is easier) and *conceptual fluency* (the fact that processing a stimulus is facilitated by the pre-activation of a related concept) may contribute differentially to familiarity (Jacoby & Dallas, 1981; Rajaram & Geraci, 2000; Wagner & Gabrieli, 1998; Whittlesea, 1993; Whittlesea & Williams, 2000, 2001a, 2001b). However, fluency per se is thought not be sufficient to support recognition judgement (Conroy, Hopkins, & Squire, 2005; Graf, Squire, & Mandler, 1984; Hamann & Squire, 1997; Levy, Stark, & Squire, 2004) and an explicit *process of attribution* of this fluency to previous experience may be necessary to support familiarity, and therefore performance on recognition

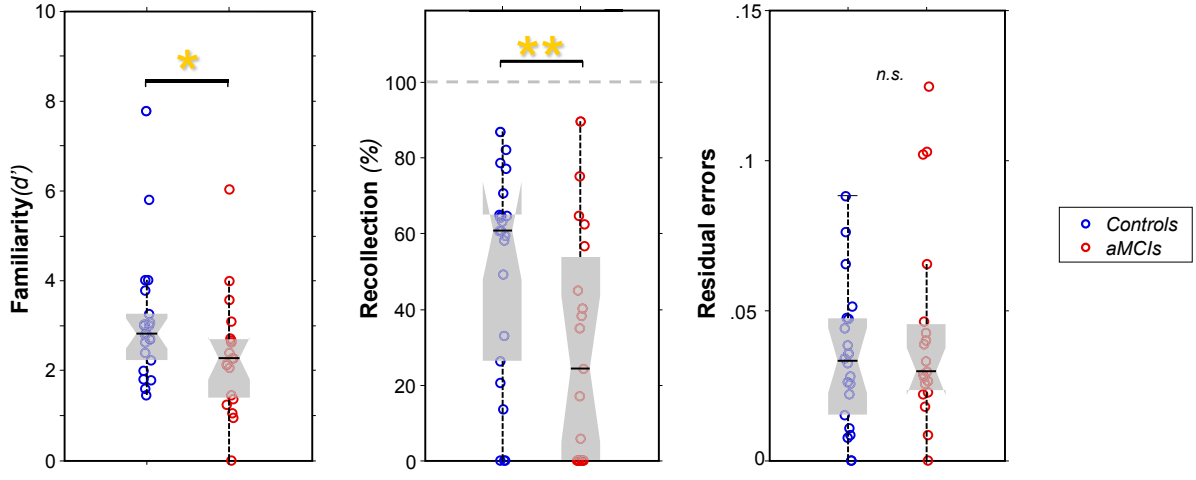


**Fig. 4 – Familiarity, recollection and residual errors as estimated using the YHT model from ROC data in task 1.**

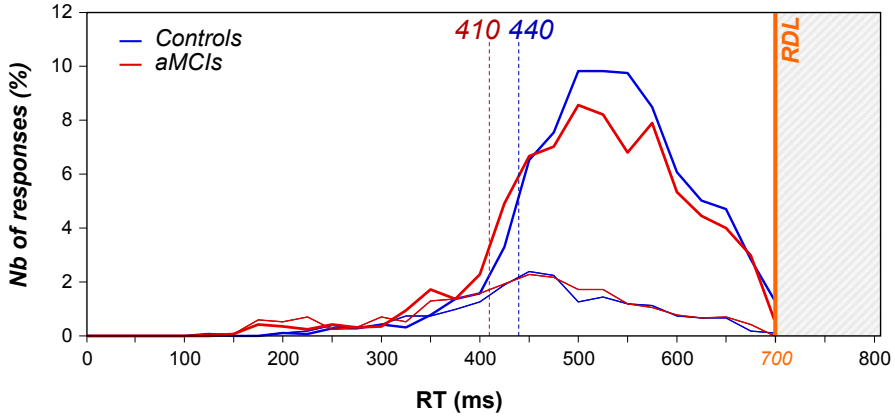


**Fig. 5 – Across trials reaction time distributions of Hits (thick lines) and False alarms (thin lines). Vertical dotted lines represent across trials minimal reaction time. RDL = Response Deadline.**

memory tasks (Jacoby & Whitehouse, 1989; Whittlesea, 1993; Whittlesea, Jacoby, & Girard, 1990; Whittlesea & Williams, 2001a). Another process likely to be involved in familiarity is *post-retrieval monitoring* (see relevant Evoked-Related Potential literature on the Late Frontal Effect, Curran, Schacter, Johnson, & Spinks, 2001; Donaldson & Rugg, 1999; Ranganath & Paller, 2000). Moreover, familiarity can also be viewed as a first-order representation about the world (i.e., a signal indicating a sense of prior exposure) or a second-order representation corresponding to the moment when a subject becomes aware of this first-order representation (Dienes, Scott, & Wan, 2011). Overall, the present results, apparently contradicting the classical view of a single-process familiarity, confirm that familiarity relies on a variety of subprocesses, each with its own temporal signature although the exact sequence remains to be determined.

Normal performance in aMCI patients on the SAB may be related to the fact that the patients over-rely on perceptual fluency because the SAB is run with strong time pressure. This is in line with evidence to suggest that perceptual fluency is likely to be preserved in aMCI patients, as demonstrated in a large study including 190 single-domain aMCI, for both verbal and visual material (Perri, Serra, Carlesimo, & Caltagirone, 2007), a finding that was confirmed by other studies (Brambati, Peters, Belleville, & Joubert, 2012; Galli et al., 2010; O'Connor & Ally, 2010) and also observed in patients with mild Alzheimer's disease (Bastin, Willems, Genon, & Salmon, 2013; see also Willems, Salmon, & Van der Linden, 2008). Further evidence suggests that aMCI patients over-rely on fluency for their recognition memory judgements, as if a neocortical system had been released from hippocampal control in these patients (Gold, Marchant, Koutstaal, Schacter, & Budson, 2007; Willems, Germain, Salmon, & Van der Linden, 2009). Moreover, several studies provide evidence for compensatory mechanisms involving anterior subhippocampal structures, which could facilitate processes relying on these structures (Dickerson et al., 2004; Gour et al., 2011).

Within this context, and considering the rapidity of the responses (the minimal reaction time in aMCI patients was 410 msec across trials and 480 msec across subjects), the question arises whether succeeding the SAB requires the participation of explicit recognition memory at all (e.g., involving a process of attribution) because it has been suggested that implicit memory processes – such as perceptual fluency – could drive behaviour directly during recognition memory tasks, without the awareness of retrieval that characterizes explicit memory (Ko, Duda, Hussey, & Ally, 2013; Voss et al., 2012). This phenomenon, called *implicit recognition*, can occur in particular circumstances when participants have no confidence in their memory, and are asked to "guess". However, that performance on the SAB depends exclusively on implicit processes is questionable, since it relies on explicit instructions both during encoding and recognition. Participants in a previous study in young healthy participants using the SAB were perfectly able to report on the subjective state (i.e., familiarity or recollection) that their answers were based on, and reported very few "guesses" (Besson et al., 2012). Interestingly, the distribution of RTs over time of participants in this previous study (their Fig. 2B for objects at 600 msec) is very similar to those of both older controls and aMCIs in the present study. Accuracy on the SAB was also rather good ($d' > 1.5$ in both groups of the present study) and higher than usually reported in implicit recognition memory tasks, suggesting at least a basic access to awareness. Also, the process of attribution was found to be partly preserved in other studies in patients with aMCI (Budson, Dodson, Daffner, & Schacter, 2005; Willems et al., 2009). Altogether, although there is evidence that performance on the SAB relies on preserved implicit processes in aMCI patients, the possibility that additional explicit processes contribute to correct familiarity judgements during the SAB remains likely.

Finally, which aspect of familiarity is impaired when aMCI patients have more time then? Results using conceptual fluency tasks are contradictory since it was sometimes found to be preserved in mild Alzheimer's Disease (Wolk et al., 2005) and aMCI patients (Deason, Hussey, Budson, & Ally, 2012; O'Connor & Ally, 2010), but sometimes impaired (in aMCIs, Gong et al., 2010; in Alzheimer's disease, e.g., Fleischman et al.,

2005), with results from semantic priming experiments indicating impairment when access to detailed information is required (Brambati et al., 2012; Giffard et al., 2001, 2002). The late frontal effect associated with post-retrieval monitoring has been reported to be preserved in aMCIs for pictures (Ally, McKeever, et al., 2009), but it remains unclear whether this effect reflects the integrity of post-retrieval monitoring per se, since the contrast used (hits vs correct rejected trials) could assess more "retrieval success" than "retrieval attempt" (extending a reasoning proposed recently by Wolk et al., 2013 on the FN400 and familiarity assessment in aMCIs). Furthermore, the results of the present study show that aMCI patients had lower confidence than control subjects in their response in the unspeeded paradigm (Fig. 3). Therefore, conceptual fluency, *and* post-retrieval monitoring, *and* confidence assessment, *and* even access to awareness (i.e., second-order familiarity as suggested by Dienes et al., 2011) are candidates of the late processes underpinning familiarity that may be dysfunctional in aMCI. Although the present study is not able to assess which of the processes is impaired, as it was not designed for this purpose, it clearly indicates that future studies should investigate this aspect of familiarity in aMCIs.

There may be limits to this interpretation however as the yes/no and SAB tasks in the present study differed concerning the paradigm used (yes/no *vs* go/no-go). The use of a go/no-go paradigm is inherent to the SAB which aims at assessing reaction times under strong time pressure in order to assess familiarity. In contrast, the use of a yes/no paradigm with confidence responses was made on purpose to replicate previous findings that both performance and recollection would be impaired in aMCI patients. The two tasks also differed on the length of the distracting phase (15 *vs* 3 min). The yes/no task was indeed easier than the SAB. Hence, we increased the delay between the encoding and test phases to make it more comparable to the SAB. Despite this increase, the yes/no task remained easier than the SAB for both control subjects and patients with aMCI. This is interesting, however, as this appears to rule out the simple idea that familiarity was impaired in aMCI patients in the yes/no task due to the increased delay between encoding and test. Indeed, it would be difficult to explain why familiarity was impaired in the easy task and preserved in the more difficult one.

These results may contribute to a better understanding of why some studies found preserved while others found impaired familiarity in patients with aMCI. As a wide variety of tasks has been used, some of the studies reporting preserved familiarity may simply have incidentally relied heavily on the processes preserved in familiarity (e.g., preserved perceptual fluency for pictures in Westerberg et al., 2013). Also, some studies have assessed patients with multiple- rather than single-domain aMCI, and other possible confounding factors such as word/picture distinct effects may also have played a role (Embree et al., 2012; Wolk et al., 2013), for these conflicting results in this rather recent field of research. Moreover, as aMCI patients are heterogeneous in terms of disease severity and underlying pathology, although most patients ultimately develop dementia (Petersen, 2013), it will be interesting to assess whether patients meeting criteria for MCI due to AD (Albert et al., 2011) show the profile of deficit found in the present study.

The present findings may have a broad impact since they reveal a within-group dissociation suggesting that familiarity may result from the combination of a set of subprocesses, each with its own temporal signature. They indicate that a very basic component of declarative memory, probably at the interface between implicit and explicit memory, may be preserved in aMCI patients with an objective memory impairment. It is specifically suggested that familiarity based on early processes contributing to familiarity is intact, while familiarity using all processes available over a longer period of time is impaired in aMCI patients. Although this unfortunately suggests that memory support programs cannot rely on the full preservation of familiarity, it could mean that it is possible to design support programs based on the "first impression" in aMCI patients. However, further studies are needed to ascertain under which conditions speeded recognition memory tasks are preserved in aMCI.

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