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The effects of healthy aging, amnestic mild cognitive impairment, and Alzheimer's disease on recollection, familiarity and false recognition, estimated by an associative process-dissociation recognition procedure

Alfonso Pitarque [a,*], Juan C. Meléndez [a], Alicia Sales [a], Teresa Mayordomo [a], Encar Satorres [a], Joaquín Escudero [b], Salvador Algarabel [a]

[a] University of Valencia, Spain
[b] Department of Neurology, General Hospital, Valencia, Spain

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ABSTRACT

Given the uneven experimental results in the literature regarding whether or not familiarity declines with healthy aging and cognitive impairment, we compare four samples (healthy young people, healthy older people, older people with amnestic mild cognitive impairment – aMCI –, and older people with Alzheimer's disease – AD –) on an associative recognition task, which, following the logic of the process-dissociation procedure, allowed us to obtain corrected estimates of recollection, familiarity and false recognition. The results show that familiarity does not decline with healthy aging, but it does with cognitive impairment, whereas false recognition increases with healthy aging, but declines significantly with cognitive impairment. These results support the idea that the deficits detected in recollection, familiarity, or false recognition in older people could be used as early prodromal markers of cognitive impairment.

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1. Introduction

Research on the neurobiology of memory has led to the proposal that there are different forms of memory supported by different neural structures. According to the *dual-process* theories (e.g. Koen and Yonelinas, 2014; Schoemaker et al., 2014; Yonelinas, 2002), memory for a past experience can be based on a conscious *recollection* of contextual details from that experience or on an automatic estimation of the strength of that memory trace in the absence of contextual details (a sense of "déjà vu" or *familiarity*). These models assume that, whereas recollection is impaired in normal aging, familiarity is spared (e.g. Koen and Yonelinas, 2014; Prull et al., 2006; Yonelinas, 2002), or at least it is less affected than recollection (Koen and Yonelinas, 2016). The neural substrates of recollection and familiarity seem to be neuro-anatomically dissociated within the medial temporal lobe regions: recollection has been linked to hippocampal function, while familiarity appears related to perirhinal cortex activity (e.g. Yonelinas et al., 2010). In contrast to the dual-process models, the *single-process* theories (also called *signal-detection* or *global strength* theories; e.g. Dunn, 2004) propose that recognition is based only on a quantitative estimation of the strength of the memory trace: what dual models call recollection would refer to strong memories, while familiarity would be considered weak memories, with the hippocampus being the neural substrate for both types of memories (Wixted and Squire, 2010, 2011).

The processes of familiarity and recollection have mainly been analyzed through three types of experimental procedures (see e.g. Koen and Yonelinas (2014), Schoemaker et al. (2014) and Yonelinas (2002), for an explanation): the remember-know (RK) paradigm, the process-dissociation procedure (PD), and the analysis of recognition memory receiver operating characteristics (ROC). Two recent literature reviews (Koen and Yonelinas, 2014; Schoemaker et al., 2014) have shown that there is unanimity in accepting that recollection declines in both healthy aging (Koen and Yonelinas, 2014, 2016) and cognitive impairment (in patients with amnestic mild cognitive impairment – aMCI – and Alzheimer's Disease – AD –; Schoemaker et al., 2014). In fact, on screening tasks, recollection deficits are usually taken as the key prodromal marker for the early diagnosis of pathological cognitive impairment (Petersen and Morris, 2003).

However, the experimental results related to familiarity are not conclusive and differ depending on the experimental paradigm used and the degree of cognitive impairment. Thus, in healthy aging, familiarity does not seem to be impaired in studies using

* Correspondence to: Department of Methodology, Faculty of Psychology, University of Valencia, Av. Blasco Ibanez 21, 46010 Valencia, Spain.
E-mail address: pitarque@uv.es (A. Pitarque).

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ROC or PD methods, but it is impaired in studies that use the RK procedure (see the recent meta-analytic review by Koen and Yonelinas (2014); however, Koen and Yonelinas (2016), recently found converging evidence for a preservation of familiarity using the three procedures in a sample of older adults). With regard to familiarity in aMCI patients, results are even less consistent. In their recent review, Schoemaker et al. (2014) found six studies that demonstrated a decline in familiarity, whereas five studies indicated preservation. In AD patients, both recollection and familiarity were affected (Schoemaker et al., 2014). Based on these results, some authors defend the idea of also using familiarity deficits as early markers of cognitive impairment (see, e.g., Koen and Yonelinas (2014) and Wolk et al. (2008, 2013)).

Given these inconsistent results about the role of familiarity in cognitive impairment, we want to propose an associative recognition task that will provide a way to evaluate whether or not familiarity declines with healthy aging and cognitive impairment. On this task, subjects will have to simply decide whether pairs of images presented on the recognition test appear as they were studied earlier (*intact* pairs) or not (either because they were *rearranged* or because they are *new*). Our idea stems from recent studies by Cohn, Emrich and Moscovitch (2008), Wolk et al. (2008; exp. 1) and Wolk et al. (2013), who used the associative recognition procedure as an method for estimating both recollection and familiarity, following the logic of the PD procedure (Yonelinas and Jacoby (2012), for a recent review), given that the intact and rearranged pairs can be understood as the inclusion and exclusion conditions of the PD procedure, respectively. Based on the rate of "old" responses for intact and rearranged pairs, independent estimates of recollection (R) and familiarity (F) can be calculated based on the following (Wolk et al., 2008, 2013):

$$R = \text{probability}(\text{intact}) - \text{probability}(\text{rearranged});$$

$$F = \text{probability}(\text{rearranged})/(1-R).$$

To account for differences between samples in their base rates of false alarms ("old" responses to new pairs –FAN-), familiarity should be corrected by subtracting each participant's FAN from his or her initial familiarity estimate and expressing the difference in terms of a discrimination measure (d′) derived from signal detection theory (Cohn et al., 2008; Wolk et al., 2008, 2013).

In addition, this associative recognition task will allow us to analyze the role that age and cognitive impairment play in false recognition, given that for some authors it could be considered as another early marker of cognitive impairment (e.g. Hildebrant et al., 2009a, 2009b; Yeung et al., 2013). In this way findings from several experimental paradigms provide concurrent evidence that false recognition (and false memories) increases with age in healthy older people (e.g. Buchler et al., 2011; Light et al., 2004; McCabe et al., 2009; Norman and Schacter, 1997; Rhodes et al., 2008), especially when items are perceptual or conceptually related (Yeung et al., 2013). The explanation that dual-process models provide for this is that older people, due to the decline in their recollection capacity, base their recognition less on recollecting contextual details and more on the activation of the items (e.g. Kilb and Naveh-Benjamin, 2011; Prull et al., 2006; Rhodes et al., 2008) or on the general similitude underlying the information (or *gist* memory; Reyna and Brainerd, 1995). However, several other studies have shown that false recognition is significantly lower in aMCI and AD patients than in healthy older adults (but only after controlling for the basal level of false alarms; e.g. Budson et al., 2000; Hudon et al., 2006), which has been interpreted to mean that the *gist* memory of these patients is diminished (Budson et al., 2000, 2006a; Gallo et al., 2006; Hudon et al., 2006). However, if we do not control the basal level of false alarms, these patients can show false recognition rates that are similar to or greater than those found in healthy people of the same age (e.g. Balota et al., 1999; Watson et al., 2001) because they tend to show a more liberal response bias than that of healthy older adults (e.g. Budson et al., 2006b). Therefore, to control for response bias, we will calculate the corrected false recognition rates by subtracting the proportion of "old" responses to new lure pairs (FAN) from the proportion of "old" responses to rearranged lure pairs (e.g. Abe et al., 2011; Budson et al., 2006a, 2006b; Hudon et al., 2006).

During the study task in our experiment, half of the pairs will be presented once, and half of the pairs will be presented twice, in order to manipulate the effect of pair repetition on recollection, familiarity, and false recollection (e.g. Light et al., 2004; Rhodes et al., 2008, exp. 3). It is well known that in young people, pair repetition increases the hit rates for intact pairs because it strengthens the association between the two items and increases the activation of each item, making the pair more accessible to recognition (Kilb and Naveh-Benjamin, 2011; Tussing and Green, 2001). In healthy older people, pair repetition also increases their hit rates for intact pairs, but to a lesser extent than in young people, as they show deficits in both encoding (the associative-binding deficit hypothesis; see the meta-analysis by Old and Naveh-Benjamin (2008), for a review) and in recollection-based recognition, and they tend to rely more on the activation of the items (increased by repetitions; e.g. Buchler et al., 2011). Finally, patients with cognitive impairment should show a more significant deficit in their hit rates for intact pairs because they are impaired in both recollection-based and familiarity-based recognition (Gallo et al., 2004). Nevertheless, pair repetition also increases false recognition, especially in healthy older people, as stimulus repetition increases the familiarity of the items (Tussing and Green, 2001), leading to more false alarms on rearranged pairs (Light et al., 2004; Rhodes et al., 2008). However, young adults, as their recollection-based recognition ability is intact, use practice to enhance recollection and reduce their false alarm rates on rearranged pairs (e.g., using the "recall-to-reject" strategy, which involves rejecting a non-studied XY lure pair because the participant can consciously recollect that stimulus X was associated with stimulus Z during the study task, and not with stimulus Y; see Abe et al. (2011), Cohn et al. (2008) and Gallo et al. (2004)). This "recall-to-reject" strategy, where recollection combats familiarity in young adults to reduce false recognition, has found extensive experimental support (e.g. Abe et al., 2011; Buchler et al., 2011; Cohn et al., 2008; Gallo et al., 2004; Light et al., 2004; Pitarque et al., 2015; Rhodes et al., 2008). Thus, in our laboratory we recently compared two samples of healthy older people, one with high cognitive reserve and the other with low cognitive reserve (Stern, 2009), on an associative recognition task. We found that stimulus repetition increased false recognition in the group with low cognitive reserve, but not in the group with high cognitive reserve. The interpretation of this result was that the former group based its judgments more on familiarity, while the latter group made better use of the "recall-to-reject" strategy in order to control the effect of familiarity on false alarms (Pitarque et al., 2016).

However, the experimental results about the role that stimulus repetition plays in the false recognition of patients with cognitive impairment are far from unanimous. If the aMCI and AD patients mainly base their decisions on the familiarity of the items, they would also be expected to increase their rates of false recognition with stimulus repetition, and this is precisely what has been shown in studies like those by Abe et al. (2011), Budson et al. (2000) or Gallo et al. (2004). By contrast, other studies have shown that repetition does not affect false recognition in AD patients (see e.g. Budson et al. (2002) and Schacter et al. (1998)), which has been interpreted as indicating that these patients also seem to

have a deficit in their *gist* memory. Given this disparity in the experimental data, our procedure will also allow us to analyze the effects of repetition and healthy and pathological aging on false recognition.

In summary, we propose an associative recognition experiment (recognition of faces associated with everyday scenery; e.g. Kilb and Naveh-Benjamin, 2011, exp. 2) in which half of the pairs are repeated during the study task. This procedure will allow us to obtain corrected estimates of recollection, familiarity and false recognition. We will compare three samples of older people (with 30 people in each): one with healthy people, another with aMCI patients, and the third with AD patients, matched on gender, age, cultural level, verbal intelligence and depressive symptomatology. A control group of healthy young people (N =42) is also included to serve as a baseline to show the optimal level of memory performance. Our main objective is to analyze whether familiarity declines with healthy aging (comparing the samples of young and older healthy people) and whether it declines with cognitive impairment (comparing the samples of healthy older people vs aMCI and AD patients), given the contradictory experimental data found in the literature. We also intend to analyze whether the false recognition of the aMCI or AD patients increases, remains the same, or declines with the stimulus repetition, compared to what is found in healthy older people, given the uneven experimental results reviewed. The results will allow us to analyze whether familiarity and false recognition could be used, along with recollection deficits, as early markers of cognitive impairment.

2. Material and methods

2.1. Participants

We compare four samples of volunteers consisting of: 42 young people, 30 healthy elderly people, 30 amnestic mild cognitively impaired (aMCI) older individuals, and 30 Alzheimer's disease (AD) diagnosed patients (see Table 1 for demographic and neuropsychological data). The young group was composed of undergraduates at the University of Valencia (mean age =22.14 years, SD =3.21, range 18–30 years old). The healthy elderly participants were recruited from various senior citizen centers in the city of Valencia (mean age =75.83 years, SD =5.63, range 67–90 years old). The aMCI and AD elderly participants were patients from the Neurology Department of the General Hospital of Valencia (aMCI group mean age =77.07 years, SD =6.50, range 64–91 years old; AD group mean age =80.03 years, SD =6.49, range 64–93 years old). The three samples of older people were matched on gender, age, cultural level, intelligence and depressive symptomatology (see Table 1). Patients in the aMCI group met the diagnostic criteria specified by Petersen (2004) and were all amnestic patients (ergo with memory deficits; see Table 1). Amnestic MCI patients have been found to be at a greater risk of conversion to AD than their non-amnestic counterparts (Schoemaker et al., 2014). Clinical diagnosis was the end-result of an extensive evaluation, including medical history and physical and neuropsychological examinations, and it was determined by consensus between neurologists and a neuropsychologist. Exclusion criteria for patients were: significant asymptomatic neurovascular disease, a history of previous symptomatic stroke, any medical condition significantly affecting the brain, serious psychiatric symptoms, or a history of drug abuse. All participants (or close family members) gave written informed consent for the study. The study was approved by the institutional review board of the General Hospital of Valencia and the University of Valencia.

All the participants performed the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997). All the elderly people (both healthy and cognitively impaired) underwent the following psychometric evaluation (see Table 1): the Mini-Mental State Examination (MMSE; Folstein, Folstein and McHugh, 1975), the CES-D Depression Scale (Radloff, 1997), the Spanish Verbal Learning Test (immediate and delayed; Benedet and Alejandre, 1998), and the Categorical and Phonological Verbal Fluency Test (Morris et al., 1989). Working memory was assessed with the Digit Span Forward and Backward Test (Wechsler, 1987), and visiospatial memory was assessed with the Construction Figure Complex Test (immediate and delayed; Rey, 1941).

2.2. Materials

The same materials were used as in Pitarque et al. (2015, picture pairs). They consisted of 64 ID-card sized color photographs (145 × 160 pixels) of anonymous faces (16 of older men, 16 of older women, 16 of young men and 16 of young women) linked to 64 color photographs of unknown everyday scenery (800 × 600 pixels; e.g. Kilb and Naveh-Benjamin, 2011).

2.3. Procedure

The associative recognition task consisted of a study phase with 64 pairs of pictures and a recognition task with 60 pairs, with a 5-min break between them. In the study phase, 60 pairs of stimuli (plus 2 pairs of distractors at the beginning and at the end, not tested later) were presented randomly at the center of a computer screen for 2.5 s each (with a 1-s interval between them). On the study task, 20 pairs were presented once, and 20 pairs were presented twice. Participants were instructed to learn both the

Table 1
Means (and SE) of demographic and neuropsychological data.

	a. YOUNG (n=42)	b. HEALTHY OLDER (n=30)	c. aMCI (n=30)	d. AD (n=30)	significant differences ($p < .05$)
Age	22.14 (.50)	75.83 (1.03)	77.07 (1.19)	80.03 (1.19)	a < (b = c = d)
Gender (male/female)	14/28	7/23	10/20	7/23	
Education (1–4 scale)	4.00 (.00)	2.47 (.23)	2.10 (.14)	2.03 (.12)	a > (b = c = d)
WAIS Vocabulary	9.05 (.39)	11.33 (.44)	12.27 (.46)	11.47 (.61)	a < (b = c = d)
Mini Mental (MMSE)	not applicable (n.a.)	28.40 (.28)	24.83 (.82)	20.53 (.67)	b > c > d
Depression Scale (CES-D)	n.a.	14.22 (.43)	12.33 (.35)	13.17 (.26)	
Verbal Learning Test Immediate	n.a.	48.40 (.42)	27.25 (.26)	16.53 (.24)	b > c > d
Verbal Learning Test Delayed	n.a.	10.20 (.10)	4.00 (.12)	1.36 (.09)	b > c > d
Verbal Fluency Test Categorical	n.a.	21.20 (.22)	15.28 (.13)	9.23 (.14)	b > c > d
Verbal Fluency Test Phonological	n.a.	31.7 (.36)	22.60 (.17)	15.36 (.24)	b > c > d
Digit Span Test Forward	n.a.	7.40 (.04)	7.28 (.06)	6.20 (.05)	(b = c) > d
Digit Span Test Backward	n.a.	4.00 (.06)	3.37 (.04)	2.20 (.05)	(b = c) > d
Visual Memory Test Immediate (Rey)	n.a.	34.00 (.09)	27.57 (.32)	15.56 (.38)	(b = c) > d
Visual Memory Test Delay (Rey)	n.a.	11.25 (.08)	6.21 (.25)	.93 (.10)	b > c > d

pictures and their pairings for a subsequent memory task, and they were told that some pairs would be repeated.

In the recognition phase (self-paced), 60 pairs of stimuli were presented randomly at the center of a computer screen. The participants just had to decide whether or not the two pictures in each pair had appeared together in the study task; that is, participants should only respond "yes" to intact pairs. Of the 60 pairs of stimuli presented, 10 corresponded to the *non repeated intact* condition, 10 corresponded to the *repeated intact* condition, 10 corresponded to the *non repeated rearranged* condition (randomly re-matching the stimuli in a different order from the one studied), 10 corresponded to the *repeated rearranged* condition, and 20 corresponded to the *new* condition (pairs of pictures not seen during the study phase).

3. Results and discussion

We began by analyzing false alarms (FA) on new pairs (FAnew; see Table 2) to analyze whether there were significant differences between groups in their basal FA level. A one-way analysis of variance (ANOVA) comparing the four groups' means showed that the effect of the groups variable was significant ($F_{3,128}=19.21$, $p<.0001$, $\eta_p^2=.31$). Post-hoc Bonferroni *t*-tests showed that young people (mean =.00) made significantly fewer FAnew than the other groups, among which there were no significant differences (means =.14, .23 and .24, for the healthy older, aMCI, and AD samples, respectively). These results show that the basal level of FAnew differs between young and older people (both healthy and patients), which is commonly found in the literature (see, e.g., Gallo et al. (2004), Pitarque et al. (2015) and Rhodes et al. (2008)). Therefore, the following estimates of recollection, familiarity, and false recognition will have to control the different basal FA levels in each participant (e.g. Buchler et al., 2011; Light et al., 2004; Prull et al., 2006).

Recollection was estimated by calculating the individual differences between H – FArea (e.g. Cohn et al., 2008; Gallo et al., 2004; Prull et al., 2006; Rhodes et al., 2008; Wolk et al., 2008, 2013), as an index of associative memory because intact and rearranged pairs are equally familiar (in both cases, the pictures were presented for study the same number of times: 1 or 2). A mixed ANOVA of 4 groups (between subjects) × 2 repetition conditions (non repeated vs repeated stimuli, within subjects) on recollection estimates (see Table 2) showed that the main effects of both groups and repetition conditions were significant ($F_{3,128}=103.06$, $p<.0001$, $\eta_p^2=.71$; $F_{1,128}=6.42$, $p<.05$, $\eta_p^2=.05$, respectively), indicating that repeated stimuli were better recollected than non repeated stimuli (means =.33 and .26, respectively). Post-hoc Bonferroni *t*-tests comparing the four groups' means showed that the recollection capacity declines with healthy aging (young sample mean =.72 vs healthy older people mean =.26) and with cognitive impairment (as usual in literature; e.g. Schoemaker et al., 2014): the healthy older people's mean (.26) differed from both the aMCI mean (.14) and the AD mean (.05), with no significant differences between the latter two groups. One sample *t*-tests comparing each of these means against the 0 value (which indicates a null recollection capacity) confirm a null recollection capacity in the AD group (mean =.05; $t_{29}=1.32$), whereas the means of the groups of aMCI (.14) and healthy older people (.27) differed significantly from 0 ($t_{29}=2.98$, $p<.05$ and $t_{29}=5.32$, $p<.001$, respectively), which confirms that they have some recollection capacity. The interaction was not significant ($F_{3,128}=2.24$). Overall, the estimated recollection results show a clear decline in associative memory in both healthy and pathological aging, as well as a null level of associative memory in AD patients. These results coincide with what has been published in recent literature reviews using distinct experimental procedures (Koen and Yonelinas, 2014; Schoemaker et al., 2014), and they support the associative-binding deficit hypothesis (Old and Naveh-Benjamin, 2008), which proposes that older adults' episodic memory impairments are partially due to a reduced ability to encode and retrieve associated/bound units of information.

Familiarity was estimated as the index of discrimination (d′) between the FArea /(1 − R) and FAnew (e.g. Cohn et al., 2008; Wolk et al., 2008, 2013). To calculate these d′ scores, hit rates and FA rates of 0 and 1 were converted to .02 and .98, respectively, to avoid infinitely large d′ values (e.g. Cohn et al., 2008; Prull et al., 2006). Regarding this estimation of familiarity (d′; see Table 2), a mixed ANOVA 4 groups × 2 repetition conditions showed significant main effects for both the groups variable ($F_{3,128}=12.26$, $p<.0001$, $\eta_p^2=.22$) and the repetition conditions ($F_{1,128}=12.51$, $p=.001$, $\eta_p^2=.09$), indicating that repeated stimuli yielded more familiarity-based responses than non repeated stimuli (means =1.59 and 1.04, respectively). Post-hoc Bonferroni *t*-tests comparing the four groups' means showed that familiarity does not decline with age (young and healthy older people's means =1.75 and 1.81, respectively), as the dual-process models propose (Prull et al., 2006; Yonelinas, 2002). However, it does decline with cognitive impairment, as the mean of healthy older people (1.81) differs significantly from the means of the aMCI and AD patients (means =1.10 and .59, respectively, with no significant differences between them). These means (1.10 and .59) also differ significantly from the 0 value ($t_{29}=5.89$, $p<.0001$ and $t_{29}=4.43$, $p<.0001$, respectively), which indicates that both the aMCI and AD patients

Table 2
Means (and SE) of hits, false alarms (FA) on rearranged and new pairs, and corrected estimates of recollection, familiarity discrimination index (d′) and false recognition according to the groups and repetition conditions.

		YOUNG (n=42)	HEALTHY OLDER (n=30)	aMCI (n=30)	AD (n=30)
HITS	Non repeated	.75 (.03)	.65 (.05)	.50 (.04)	.41 (.05)
	Repeated	.90 (.02)	.79 (.03)	.67 (.05)	.49 (.06)
FA REARRANGED	Non repeated	.12 (.02)	.39 (.04)	.40 (.05)	.37 (.05)
	Repeated	.09 (.02)	.53 (.05)	.49 (.04)	.43 (.05)
FA NEW		.00 (.00)	.14 (.02)	.23 (.04)	.24 (.03)
RECOLLECTION	Non repeated	.63 (.04)	.26 (.04)	.11 (.04)	.04 (.04)
	Repeated	.81 (.04)	.27 (.05)	.18 (.05)	.06 (.05)
FAMILIARITY (d′)	Non repeated	1.56 (.15)	1.51 (.18)	.71 (.18)	.37 (.18)
	Repeated	1.95 (.24)	2.11 (.28)	1.49 (.28)	.81 (.28)
FALSE RECOGNITION	Non repeated	.12 (.03)	.25 (.03)	.17 (.03)	.13 (.03)
	Repeated	.09 (.03)	.39 (.03)	.26 (.03)	.19 (.03)

use familiarity efficaciously in recognition. The groups × repetition conditions interaction was not significant ($F_{3,128} < 1$), which indicates a constant increase in familiarity with the stimulus repetition in the four samples (Tussing and Green, 2001), again supporting the sensitivity of our procedure for detecting this manipulation.

Overall, these results clearly show that familiarity, in contrast to recollection, does not decline with age in healthy aging, as postulated by the dual-process models (Koen and Yonelinas, 2016; Prull et al., 2006; Yonelinas, 2002). They also provide cumulative evidence supporting a preservation of familiarity in healthy aging, considering the contradictory experimental data found in recent meta-analytic reviews (Koen and Yonelinas, 2014). For this reason, various studies propose the possibility of using training in automatized routines (such as implicit or procedural motor-skill learning) as a compensatory mechanism in elderly populations with recollection deficits (see e.g. van Halteren-van Tilborg, Scherder and Hulstijn, 2007). However, our results also clearly show that familiarity, just like recollection, declines with cognitive impairment (whether understood as aMCI or AD; e.g. Algarabel et al., 2009; Wolk et al., 2008, 2013), thus providing cumulative evidence of a decline in familiarity with cognitive impairment, considering the contradictory experimental data found in the recent review by Schoemaker et al. (2014). Therefore, our results support the idea that familiarity deficits, as occurs with recollection-type deficits, could be used as early markers of pathological cognitive impairment to discriminate between healthy older people and people with incipient cognitive impairment (Koen and Yonelinas, 2014; Wolk et al., 2008, 2013).

Finally, false recognition was estimated as the individual scores FArea – FAnew (e.g. Abe et al., 2011), which some authors consider to be an estimation of *gist* memory (e.g. Budson et al., 2006a; Hudon et al., 2006). A mixed ANOVA on these false recognition estimates (see Table 2) showed that the main effects of both groups and repetition conditions were significant ($F_{3,128} = 12.64$, $p < .0001$, $\eta_p^2 = .23$; $F_{1,128} = 12.18$, $p = .001$, $\eta_p^2 = .09$, respectively), indicating that false recognition increases with repetition (means = .17 and .23, for non repeated and repeated pairs, respectively). Post-hoc Bonferroni *t*-tests comparing the four groups' means showed that false recognition increases with healthy aging (young sample mean = .10 vs healthy older people mean = .32), but decreases with cognitive impairment: the healthy older people's mean (.32) differed from both the aMCI mean (.21) and the AD mean (.16), with no significant differences between the latter two groups. However, there are no significant differences between the young and AD means (means = .10 and .16, respectively; see below for an explanation). The interaction was also significant ($F_{3,128} = 4.01$, $p < .01$, $\eta_p^2 = .09$). Post-hoc Bonferroni *t*-tests on this interaction (see Table 2) showed that repetition increased false recognition in healthy older people (means of .25 and .39 for non repeated and repeated pairs, respectively) and aMCI patients (means of .17 and .26, respectively), but not in young people (means of .12 and .09, respectively) and AD patients (means of .13 and .19, respectively).

Overall, the results for false recognition show that it clearly increases with age in healthy older people, coinciding with what was found in other laboratories (e.g. Buchler et al., 2011; Light et al., 2004; McCabe et al., 2009; Norman and Schacter, 1997; Rhodes et al., 2008). This result supports the predictions of the dual-process models in that elderly people tend to recognize by drawing more on familiarity than young people do, as this capacity is maintained with aging, while young people use more the recall-to-reject strategy to reduce their rates of false alarms (e.g. Cohn et al., 2008; Gallo et al., 2004). However, false recognition clearly decreases with cognitive impairment (whether understood as aMCI or as AD), supporting the idea that these patients also have less *gist* memory (e.g. Budson et al., 2006a; Gallo et al., 2006; Hudon et al., 2006), which coincides with their familiarity deficits, described above. For this reason, it seems reasonable to suppose that a significant decline in false recognition in older people could be considered another early marker of cognitive impairment (e.g. Hildebrant et al., 2009a, 2009b) because it would indicate a significant deficit in their *gist* memory. The fact that young people and AD patients do not differ on their false recognition rates is probably due to two different causes: as we mentioned above, young people show a low rate of false recognition because they correctly use the recall-to-reject strategy to reduce their false alarm rates, while the AD patients show low false recognition rates because they show an overdependence on their impaired *gist* memory (Gallo et al., 2006; Hudon et al., 2006). For these two different reasons, stimulus repetition does not affect the young people or the AD patients, but it does increase false recognition in healthy older people and aMCI patients. In the latter two samples, repetition increases the familiarity of the items, and as these groups are not able to use the recall-to-reject strategy, an increase in false recognition is observed (Gallo et al., 2004).

In summary, the experimental paradigm used here has made it possible to obtain corrected estimations of recollection, familiarity, and false recognition that could be used as early markers of incipient cognitive impairment in older people. In this regard, various correlational analyses also support this idea. For example, by correlating the age of the young participants and healthy older people (n = 72: 42 young people and 30 healthy older people) with their familiarity estimations (for non repeated and repeated stimuli), we observed null correlations ($r = -.01$ and $r = .04$, respectively). However, age correlated significantly with their recollection estimations ($r = -.64$, $p < .0001$, and $r = -.75$, $p < .0001$, respectively), which indicates that familiarity is not affected by healthy aging, whereas recollection declines with it, as predicted by the dual-process models (Prull et al., 2006; Yonelinas, 2002). Likewise, in these same samples, the correlation between age and false recognition was significant ($r = .43$, $p < .0001$, and $r = .67$, $p < .0001$, for non repeated and repeated stimuli), which indicates that false recognition increases with age and repetitions, reinforcing the idea that repetition increases the familiarity of the rearranged pairs, but only young people are able to counter this familiarity by recalling the originally studied pairs (recall-to-reject strategy; Gallo et al., 2004; Light et al., 2004; Rhodes et al., 2008). In the same way, the Pearson correlations among our six predictors, shown in Table 2, and the scores of the 90 elderly people (30 healthy older people, 30 aMCI, and 30 CE) on the MMSE (Folstein et al., 1975), probably the most widely used screening questionnaire, were all positive and significant ($p < .05$; with the exception of false recognition of non repeated stimuli), indicating that in older people, increases in cognitive impairment are accompanied by decreases in their recollection, familiarity, and false recognition. Overall, these correlational results seem again to support the predictive capacity of our predictors in the early diagnosis of cognitive impairment.

In another vein, it could be argued that our results could be due to group differences in encoding strategies, some of which might not be as effective as others. In our experiment, we used the usual study instructions in the literature on associative recognition, which stipulate that all the samples have to study the pairs for the same length of time (e.g. Buchler et al., 2011; Cohn et al., 2008; Kilb and Naveh-Benjamin, 2011; Rhodes et al., 2008). Other authors, such as Gallo et al. (2004), used a self-paced study task with intentional learning instructions, where subjects had to say whether it was "easy" or "hard" to link the two words in each pair (but that, in turn, presents the possibility that each sample will study the pairs during significantly different periods of time, which might make study time a new confounding variable). The fact that

the Gallo et al. (2004) results basically coincide with ours leads us to consider that our results do not seem to depend on group differences in encoding strategies.

On the other hand, a possible limitation of our study (whose samples come from daily clinical practice) has to do with not using the physio-pathological (amyloid) or neurodegeneration biomarkers in all the participants, which would have made it possible to detect a possible aMCI subgroup that would correspond to prodromal Alzheimer's disease, according to the criteria of the International Working Group (Dubois et al., 2007). These patients without amyloid deposition may not display the expected declines in familiarity and false recognition if their medial temporal lobe regions are less affected by the disease's progression. To maximize the interpretability of our findings, future studies comparing patients with positive amyloid biomarkers (e.g. CSF or PET) versus negative amyloid biomarkers should be performed (Dubois et al., 2014). This would make it possible to analyze the sensitivity of our markers in detecting aMCI patients with underlying AD, and in measuring the changes in disease progression.

To summarize, given the relatively small number of studies that have investigated familiarity and recollection in individuals with aMCI and AD (Schoemaker et al., 2014), our study provides cumulative support for considering familiarity and false recognition deficits as potential early markers of cognitive impairment in elderly populations. Our results agree with other recent neuroscience results suggesting that familiarity and recollection are differentially affected by normal aging and AD neuropathology, as dual-process models propose (see e.g., the model by Schoemaker at al. (2014) and Wolk et al. (2013)). Whereas recollection is impaired through all the stages of healthy aging and disease progression (due to both age-related and neuropathological changes in the hippocampal region), familiarity is preserved in normal aging, which makes older people show an over-reliance on familiarity to support accurate recognition judgments (e.g. Gallo et al., 2004). As AD neuropathology progresses, familiarity deficits begin to appear. Further research using alternative experimental procedures, estimation procedures, encoding instructions, and clinical populations (e.g. patients with or without prodromal AD) is needed before more extensively using these predictors in clinical settings.

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