

Cognitive function in normal aging and in older adults with mild cognitive impairment

Soledad Ballesteros, Julia Mayas and José Manuel Reales
Universidad Nacional de Educación a Distancia

Abstract

Background: In this study, we investigated the effects of normal and pathological (mild cognitive impairment, MCI) aging on several cognitive functions (processing speed, executive control and implicit memory). **Method:** Twenty young adults, 20 healthy older adults and 20 elders with MCI performed a series of cognitive tasks under controlled conditions. These tasks were simple and choice reaction time, the Wisconsin Card Sorting Test (WCST), and an implicit memory task for attended and unattended objects at encoding. **Results:** The MCI group showed pronounced declines in processing speed and executive control tasks. Interestingly, young and healthy older participants showed repetition priming for stimuli that were attended at encoding, but the MCI group did not. **Conclusions:** In this latter group, the lack of repetition priming for attended objects in the implicit memory task resembled that of Alzheimer disease (AD) patients and suggests an early deficit of selective attention that might be a marker of pathological aging.

Keywords: Aging, executive function, mild cognitive impairment (MCI), repetition priming, selective attention, speed of processing.

Resumen

Función cognitiva en mayores sanos y con déficit cognitivo leve. **Antecedentes:** en este estudio investigamos los efectos del envejecimiento sano y patológico (déficit cognitivo leve, DCL) en varias funciones cognitivas (control ejecutivo, velocidad de procesamiento y memoria implícita). **Método:** veinte adultos jóvenes, 20 mayores sanos y 20 mayores DCL realizaron una serie de tareas cognitivas bajo condiciones controladas. Estas tareas fueron tiempo de reacción simple y de elección, el Test Wisconsin y una tarea de memoria implícita para objetos atendidos y no atendidos durante la codificación. **Resultados:** el grupo DCL mostró declives pronunciados en las tareas de velocidad de procesamiento y de control ejecutivo. Además, los jóvenes y los mayores sanos mostraron priming para los objetos atendidos durante la codificación estimular, pero no los mayores con DCL. **Conclusiones:** en este último grupo, la falta de priming de repetición para objetos atendidos en la tarea de memoria implícita fueron similares a los de los enfermos de Alzheimer (EA) y sugieren la existencia de un déficit temprano de la atención selectiva en mayores DCL, lo que podría ser un marcador del envejecimiento patológico.

Palabras clave: atención selectiva, envejecimiento, déficit cognitivo leve (DCL), función ejecutiva, *priming* de repetición, velocidad de procesamiento.

As humans age, many declines occur in the cognitive system. The speed at which information is processed, inhibitory function and episodic memory (Baltes & Lindenberger, 1997; Salthouse, 1996) all show age-related declines. In contrast, verbal abilities (Craik & Salthouse, 2000) and implicit memory are age-invariant (Ballesteros & Reales, 2004; Ballesteros, Reales, & Mayas, 2007; Osorio, Fay, Pouthas, & Ballesteros, 2010; Sebastián & Ballesteros, 2012). Declines in episodic memory are more pronounced in free-recall than in recognition tasks (Gutchess & Park, 2009).

The decrease in prefrontal grey matter volume has been related to perseveration on the Wisconsin Card Sorting Task –WCST (Raz, Rodrigue, & Acker, 2003). A dorsal prefrontal attention system seems crucial for maintaining focused attention and inhibitory

control (Eckert, 2011). Moreover, elevated frontal activity with age is a well-established finding in functional imaging studies (Duverne, Habibi, & Rugg, 2008; Reuter-Lorenz & Lustig, 2005). Electrophysiological studies have shown additional frontal recruitment in highly educated older adults compared to young adults when performing a verbal cued-recall task (Osorio, Ballesteros, Fay, & Pouthas, 2009). Furthermore, older adults recruit more brain resources than young adults in a haptic object recognition task. The ERP late negativity-going activity and the greater power reduction in alpha activity suggest age-related changes in brain dynamics in voluntary information retrieval in normal aging (Sebastián, Reales, & Ballesteros, 2011).

MCI is characterized by cognitive declines that are greater than expected for a given age and educational level but it does not interfere notably with daily life activities. Some older adults with MCI remain stable or return to normal over time, but this condition is considered as a risk state for dementia, as more than half of the adults diagnosed with MCI progress to dementia within five years (Peterson, 2011). The MCI syndrome, considered as a transition stage between normal aging and dementia (Gauthier, Reisberg,

Methods

Zaudig, Petersen, Ritchie et al., 2006), has increased awareness that memory complaints should be considered closely (Dannhauser et al., 2008; Nordahl et al., 2005). However, selective attention may fail before dementia is diagnosed (Parasuraman & Haxby, 1993; Vasquez et al., 2011). The lack of attention at encoding impairs performance on episodic memory tasks (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Dannhauser, Walker, Stevens, Lee, Seal, & Shergill, 2005), but implicit memory, assessed by showing repetition priming effects (faster and/or more accurate responses to repeated than to novel stimuli), is not automatic and requires attention at encoding. Interestingly, patients with Alzheimer's disease (AD) do not show priming for attended stimuli when attended and unattended stimuli are presented at encoding, which suggests an early deficit of attention in AD (Ballesteros, Reales, Mayas, & Heller, 2008).

The aim of the present study was twofold. First, we wished to investigate the effect of normal aging and MCI on the cognitive functions mediated by the brain regions that deteriorate the most with age (lateral prefrontal cortex, hippocampus and temporal regions; Raz et al., 2005) such as executive control, speed of processing and controlled processing. We expected age-related declines in tasks mediated by frontal and temporal regions, especially in the MCI group, and little or no decline in normal aging in a repetition priming task for attended and unattended stimuli. The second aim was to investigate whether the performance of patients with MCI on the implicit memory task when attention was compromised at encoding was similar to that of AD patients, or whether it resembled that of normal elders. Visual implicit memory is mediated by posterior occipito-temporal regions (Schacter, Wig, & Stevens, 2007), which show little age-related deterioration when stimuli are fully attended at encoding. We expected similar repetition priming effects in young and healthy older adults for attended stimuli. The finding of no repetition priming for attended stimuli in MCI would suggest that attention is compromised at an early stage of pathological aging. It is important to validate this pattern, as the likelihood of suffering MCI increases with age (Sliwinski, Lipton, Buschke, & Stewart, 1996). Although there is currently some debate about how to define the syndrome, a percentage of adults with MCI might be at risk of developing clinically diagnosed AD (Bennett et al., 2002; Peterson et al., 2001).

In sum, in this cross-sectional study we investigated age-related changes in executive control, speed of processing and memory functions in young adults, elderly healthy adults and elderly adults with MCI. We expected larger declines in the MCI group than in the two healthy groups in all tasks. In the implicit memory task, the finding of no repetition priming for stimuli that were attended at encoding might be a marker of pathological aging.

Participants

Sixty volunteers were recruited based on age and performance on several screening tests. Twenty were older adults with MCI (10 women; age range 67 to 80 years), 20 were younger adults (8 women; age range 21 to 28 years) and 20 were healthy older adults (8 women; age range 65 to 75 years). All participants signed an informed consent form, had normal or corrected-to-normal vision, and had Spanish as their native language. They reported being free of cardiovascular disease and neurological disorder and were not taking medication that could influence the central nervous system. The demographic characteristics and test scores are shown in Table 1.

The young adults were undergraduate students who participated for course credit. The MCI participants were selected from several local community centres. The inclusion criteria were Mini-Mental State Examination (MMSE) scores of 24 to 26, an overall score on the Barcelona Scale (Peña-Casanova, 1991) lower than 90, with a cognitive profile of memory failures. Older participants were able to perform daily living activities. The healthy older adults were community-dwelling volunteers with normal performance on the screening tests and questionnaires (>28 on the MMSE; scores lower than 1 on the Reisberg Global Deterioration Scale (GDS), and between 0 and 1 on the Blessed Dementia Scale). After completing the screening tests, all participants performed the experimental tasks individually in a quiet room. They performed two processing speed tasks designed to assess simple and choice reaction time, a computerized version of the Wisconsin task, and a repetition priming task to assess implicit memory. Participants were seated at a distance of approximately 50 cm from the computer screen. All the experimental tasks with the exception of the Wisconsin task (Heaton, 1981) were programmed with E-prime 1.11. The study was approved by the Ethical Committee of the institution and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Experimental Tasks

Speed of processing (simple and choice reaction time) tasks. With advancing age, the speed with which many mental operations are executed decreases, and this is considered to be the main mechanism accounting for the age-related decline in most cognitive tasks (Salthouse, 1996). Participants in the study performed a simple reaction-time (RT) task and a choice RT task to assess processing speed and controlled processing, respectively.

Stimuli and procedure. In the simple RT (detection) task, the target was the letter "X". In the choice RT (selection) task the

Table 1
Demographic data and mean test scores corresponding to young adults, healthy older adults and MCI

	Age	Education	MMSE	Yesavage	Blessed	GDS
Young adults	26.25 (1.68)*	17.15 (0.98)*	29.65 (0.49)	0.7 (0.8)	0.25 (0.44)	0 (0.8)
Healthy elders	69.15 (83.15)*	13.75 (1.80)*	29.4 (0.68)	0.55 (0.68)	0.20 (0.41)	0 (0)
MCIs	74.52 (3.94)*	12 (0.81)*	24.7 (1.03)	0 (0)	1.7 (0.57)	0 (0)

Note: * $p < 0.05$; Standard deviation (SD). MMST (Mini Mental State Examination (/30)); Yesavage (Geriatric Depression Scale GDS); Blessed (Blessed Dementia Rating Scale BDRS); GDS (Global Deterioration Scale GDS)

targets were the letters “X” and “O”. The target was displayed in the center of the computer screen (in font Times New Roman, size 20). The order of tasks was counterbalanced across participants. The task started with a practice block with visual feedback. Each trial consisted of a fixation point (1000 ms), followed by a blank screen displayed for 500 ms or 1000 ms (randomly selected) after which the target (“X” in the simple RT task and “X” or “O” in the choice RT task) was presented in the center of the computer screen until the participant responded or for a maximum of 5000 ms. The inter-trial interval lasted 750 ms. In each task, there were four experimental blocks of 30 trials each, giving a total of 120 trials. In the RT task, participants pressed the “m” key of the computer keyboard as soon as they detected the target “X” using the index finger of their dominant hand. On 10% of the trials, the target was not presented (catch trials). In the choice RT task, participants pressed the “z” key when the target “X” appeared on the screen and the “m” key when the target “O” appeared, using their index fingers.

We used a mixed-factorial design with Group (young adults, healthy older adults, and MCI older adults) as the between-subjects factor and Speed task (detection and selection) as the within-subjects factor.

The Wisconsin Card Sorting Task (WCST). To assess executive control, participants performed the WCST. Neuropsychologists use this task to assess the integrity of frontal lobe functions (Milner, 1963). Perseveration on the same response suggests a failure of the executive control function. Age-related increases in the number of perseverative errors have been associated with shrinking of the prefrontal cortex and integrity of frontal areas (Gunning-Dixon & Raz, 2003).

Stimuli and procedure. Participants performed the computerized WCST: CV4 (Heaton, 1981) individually. The task consisted of matching a card that appeared in the lower right corner of the computer screen with one of four cards that appeared at the top. They had to work out the sorting category based on the computer feedback (*Correct* or *Incorrect*). Each response card could match a stimulus card on the basis of one or more dimensions. The following dependent measures were computed for each participant: percentage of errors, percentage of perseverative responses, percentage of perseverative errors, and percentage of non-perseverative errors.

Implicit memory task. To assess implicit memory, we used a study-test paradigm. Priming was assessed with a *Picture Fragment Completion task* (PFC).

Stimuli and procedure. The stimuli were 90 outline pictures drawn from Snodgrass and Vanderwart’s (1980) picture set. The drawings (about $10 \times 10 \text{ cm}^2$) subtended a visual angle of approximately 4×4 degrees and were presented on a color monitor with a resolution of 640×480 pixels. During the study phase, there were 30 trials with 30 pairs of green and blue outlines of familiar objects displayed on a white background, plus five trials at the beginning and five at the end to avoid primacy and recency effects (see Figure 1). In half of the trials, the blue object appeared on the right. At the beginning of each trial, the participant pressed a key and a fixation cross appeared at the center of the screen for 500 ms. After 1000 ms, the outline drawings of two familiar objects appeared for another 1000 ms. One outline picture was in green (the attended picture) and the other in blue (the unattended picture). One picture outlines was presented on the right and the other on the left of the centre of the computer screen.

After naming the green (attended) object as soon as possible, the next trial started. This encoding phase was followed by a 5-min filler task in which participants named as many famous people as they could think of.

In the test phase, the stimuli were fragmented outlines of the pictures displayed in black on a white background. For picture fragmentation, a 16×16 pixel grid was superimposed on the projected image. All of the 16×16 pixel blocks that contained some black pixels were identified. The information was stored in an array and was randomly permuted. Each picture was stored as a fragmented image at eight different levels of completion. Level 1 corresponded to the most fragmented image (containing less pixel information) while level 8 corresponded to the complete picture. The proportions of deleted pixel blocks were 0.91, 0.88, 0.83, 0.76, 0.65, 0.51, 0.30, and 0.00, from level 1 to level 8, respectively.

Participants identified the picture as soon as possible by pressing the spacebar of the keyboard trying to not make mistakes. The sequence stopped when the experimenter entered the participant’s correct verbal response into the computer, and a new trial started. The presentation order of the attended, unattended, and non-studied stimuli was random. Performance was assessed by the fragmentation level at which the pictures (attended, unattended and non-studied) were correctly named.

We used a 3 Group (young adults, healthy older adults, and MCIs) \times 3 Study conditions (attended, unattended, and non-studied pictures) mixed factorial design with group as between-subjects variable and study condition as within-subjects variable.

Data analysis

Performance of the three groups in each cognitive task was analysed independently. As groups differed in years of education (see Table 1), this variable was included as a covariate in the MANCOVA. This analysis was followed by repeated measures of analyses of variance (ANOVAs) on each of the tasks separately. The Greenhouse-Geisser correction was applied to the results related to within-subjects factors.

Results

Speed of Processing Tasks

The dependent variable was RT. Table 2 shows the mean RTs (SD in parentheses) of the three groups in the simple and choice reaction-time tasks. The percentage of errors on both tasks was less than 1% with no significant differences among groups. Only RTs corresponding to correct responses were included in the analyses. RTs larger than 2.5 standard deviations from the participant’s mean were also excluded from the analyses.



Figure 1. An example of the two pictures presented at the encoding phase

Table 2

Response times and SDs (in parenthesis) obtained in the Simple (Detection) and Choice reaction time tasks by young adults, healthy older adults and MCI older adults

	Simple RT (Detection) task	Choice RT task
Young adults	422 (55.63)	574 (74.45)
Healthy older adults	552 (120.84)	740 (83.49)
MCI older adults	788 (131.76)	960 (114.57)

A mixed two-factor ANCOVA with Group as the between-subject factor and Task as the within-subject factor was conducted to assess whether the three groups differed on task performance when controlling for difference in years of education. As expected, all groups were slower in the choice reaction-time task than in the simple reaction-time task as revealed by the main effect of Task, $F(1, 56) = 4.001$, $MSe = 11215.67$, $p = .05$, partial $\eta^2 = .067$. Group was significant, $F(2, 56) = 112.31$, $MSe = 9247.45$, $p < .001$, partial $\eta^2 = .80$, the young participants responding faster (498 ms) than the healthy older adults (646 ms), and the MCI (875 ms) group being the slowest (all $ps < .01$). The Group by Task interaction was not significant ($F < 1$), suggesting that differences between task conditions were comparable across groups.

Executive Functions (WCST)

A MANCOVA was conducted to assess whether there were any differences between groups from a linear combination of the percentage of errors, perseverative responses, perseverative errors, and non-perseverative errors, controlling for differences in years of education between groups. The multivariate contrast was significant for group, Wilk's $\Lambda = 0.154$, $F(18, 106) = 20.516$, $p < .001$, partial $\eta^2 = .608$] but not for the covariate ($F < 1$). Follow-up univariate ANOVAs indicated that the effect of Group was statistically significant for the percentage of errors, $F(2, 60) = 129.37$, $MSe = 25.50$, $p < .001$, partial $\eta^2 = .82$, the percentage of perseverative responses [$F(2, 60) = 89.09$, $MSe = 17.86$, $p < .001$, partial $\eta^2 = .76$, the percentage of perseverative errors, $F(2, 60) = 79.75$, $MSe = 15.64$, $p < .001$, partial $\eta^2 = .74$, and the percentage of non-perseverative errors, $F(2, 60) = 35.85$, $MSe = 56.33$, $p < .001$, partial $\eta^2 = .56$. Pairwise comparisons showed that all groups differed significantly in the percentage of errors, the percentage of perseverative responses, the percentage of perseverative errors and the percentage of non-perseverative errors ($p < 0.01$ in all cases). Figure 2 shows the means and standard deviations (SDs) of WCST scores per group.

Young adults performed significantly better than the two older groups, while the MCI group performed the worst. Poor performance on the WCST is associated with prefrontal damage (Demakis, 2003) and reduction of gray matter volume in the prefrontal cortex (Gunning-Dixon & Raz, 2003). The results

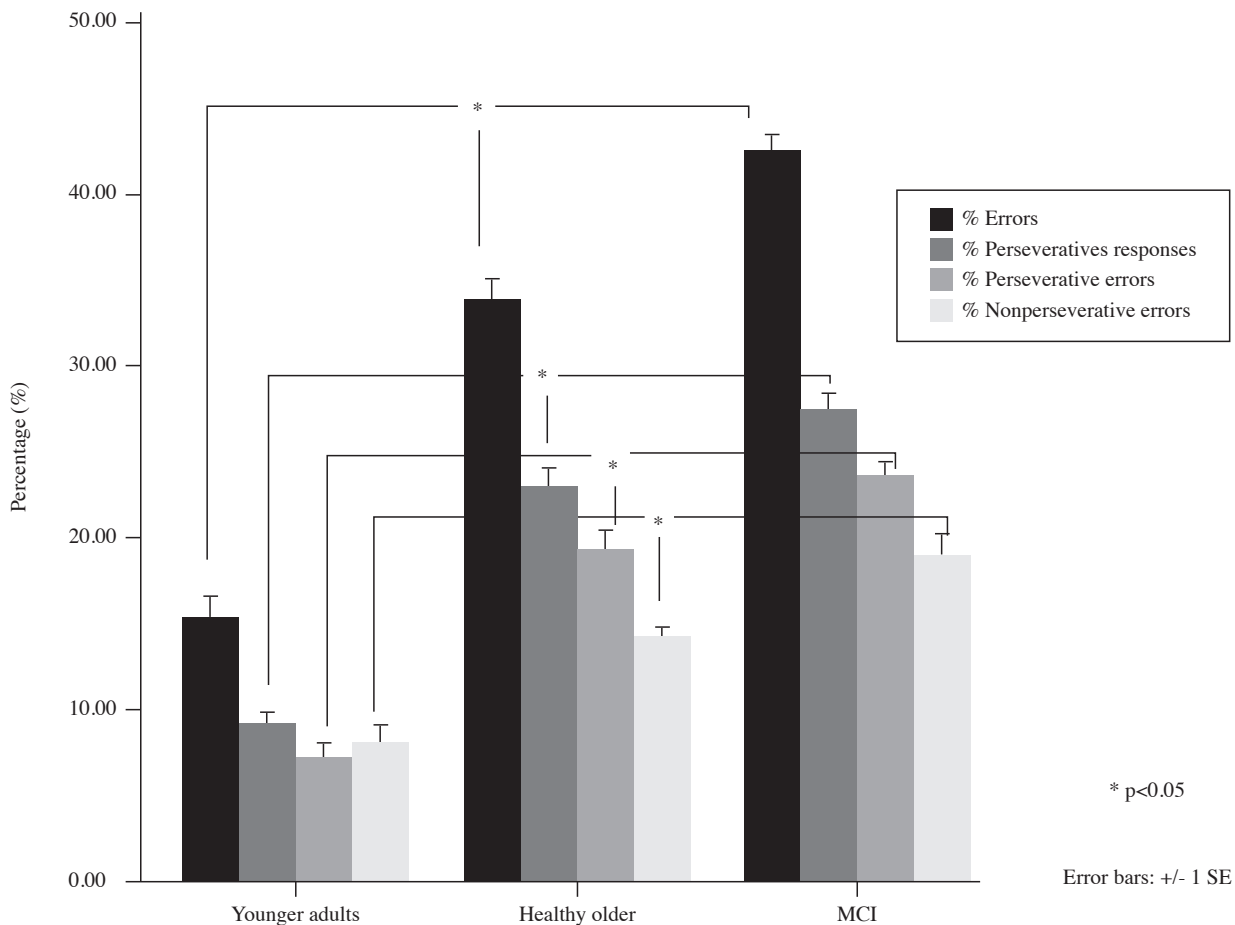


Figure 2. Mean percentage scores in the Wisconsin Card Sorting Test for young adults, older adults, and MCI older adults

suggest that executive function, especially shifting ability, decreases from adulthood to old age but the loss is much more pronounced in elderly subjects suffering from MCI (Borkowska, Drozd, Jurkowski, & Rybakowski, 2009).

Implicit Memory (Repetition Priming)

The primary measure was the fragmentation level at which the picture was identified. Figure 3 displays the mean level of completion needed to identify the stimuli as a function of group and study condition. Repetition priming is shown by the difference between the attended or unattended identification picture thresholds and non-studied (new) pictures.

The superior performance for attended pictures is shown by the lower identification threshold displayed by the two healthy groups for pictures that were attended at encoding compared to new pictures. These groups identified attended pictures at a more fragmented level than unattended and non-studied pictures but the MCI group did not. A mixed two-factor ANCOVA with Group as the between-subjects factor and Study (attended, unattended and non-studied) condition as the within-subject factor was conducted to assess whether there were any differences in task performance controlling for differences in years of education. The main effect of Group was significant, $F(2, 56) = 126.97$, $MSe = 1.13$, $p < .001$,

partial $\eta^2 = .82$. Pairwise comparisons showed that groups differed significantly at the fragmentation level at which they were able to identify the fragmented pictures. Young adults (2.915) performed better than healthy older adults, and MCI participants performed significantly worse than the two healthy groups (6.518). Study was not significant ($F < 1$) but the Group by Study interaction was statistically significant, $F(4, 112) = 4.73$, $MSe = 0.338$, $p < .01$, partial $\eta^2 = .145$ (Greenhouse-Heisser correction). Simple effect contrasts among the means showed that young and normal older groups identified attended stimuli at study at a more fragmented level than non-studied stimuli (all $ps < 0.05$). In contrast, the performance of the MCI group for attended, unattended and non-studied stimuli did not differ (all $F_s < 1$).

Discussion

The present study investigated age-related declines in normal and pathological aging (MCI) in executive control, speed of processing and memory functions, namely implicit memory assessed by a repetition priming task. Another aim was to investigate whether older adults with MCI would show similar priming for attended stimuli at encoding as normal adults or whether their performance would resemble that of AD patients who did not show repetition priming for stimuli that were attended at encoding.

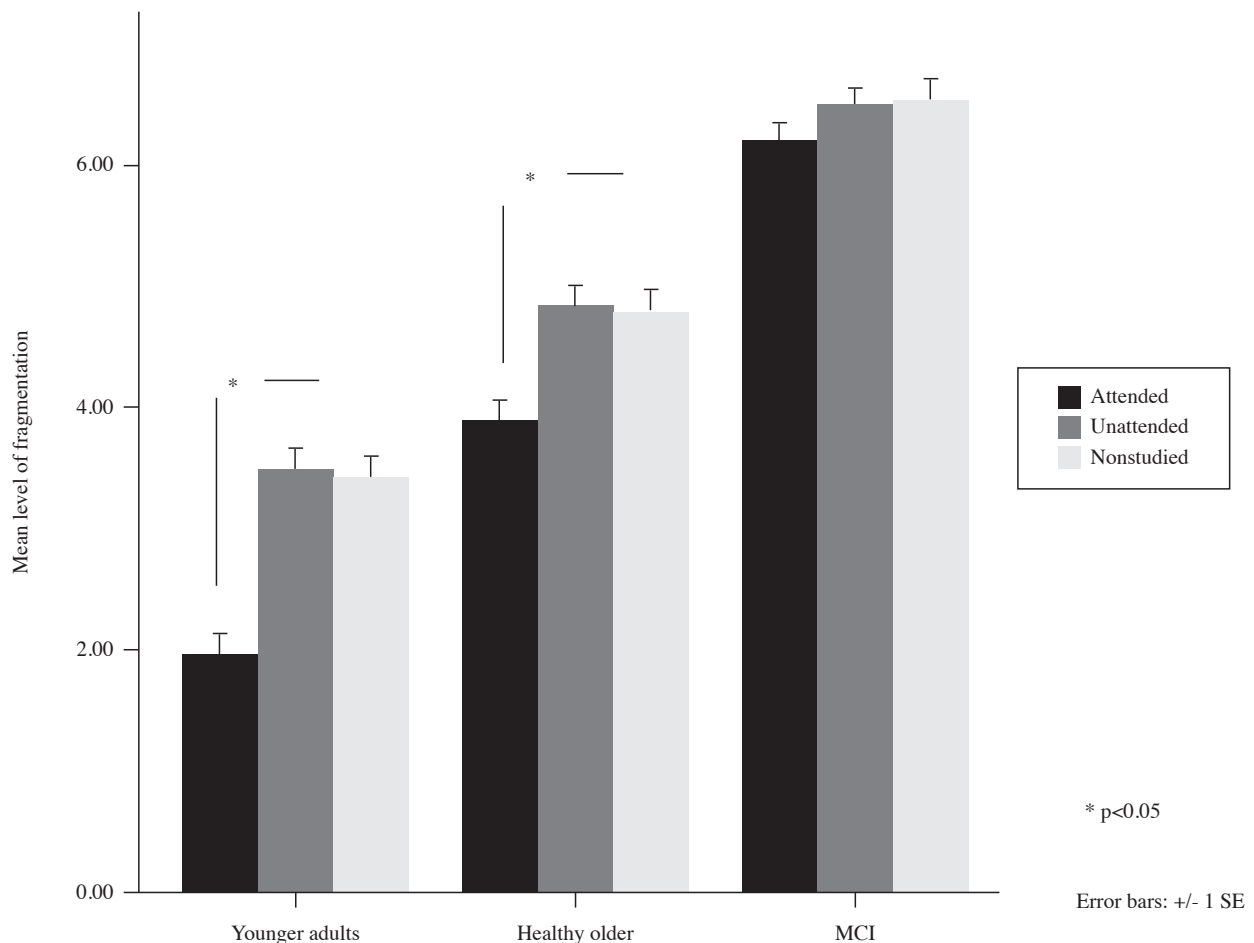


Figure 3. Mean correct identification level corresponding to attended, unattended and non-studied visual objects. Bars indicate the standard error of the mean (SEM)

The results showed age-related declines in all the WCST indexes and the speed and controlled processing tasks. Older adults were significantly slower in simple and choice RT-time tasks. Processing speed is a robust predictor of age-related cognitive decline and an indicator of independence among older adults (Salthouse & Ferrer-Caja, 2003). A large body of research (Eckert, 2011) implicated a dorsal attention prefrontal-mediated brain system for maintaining focused attention and inhibitory control in the age-related declines of processing speed that are common to many behavioral tasks that require focused attention and inhibitory control as in the WCST. In the priming task, the two healthy groups showed similar priming effects for attended stimuli at encoding. Consistent with previous findings, priming was not found for stimuli that were unattended at encoding, suggesting that implicit memory is not automatic (Ballesteros et al., 2008; Ballesteros, Reales, García, & Carrasco, 2006; Crabb & Dark, 1999; MacDonald & MacLeod, 1998). On the other hand, MCI elders did not show the priming effect for attended objects, nor did they produce a priming effect for unattended stimuli, suggesting an early deficit of selective attention and a possible marker of pathological aging (Fleishman, 2007; Vasquez et al., 2011).

Episodic retrieval requires attention at encoding (Craick et al., 1996; Rock & Gutman, 1981), but attention is also crucial for implicit memory (Ballesteros et al., 2008; Ballesteros et al., 2006; Crabb & Dark, 1999; MacDonald & MacLeod, 1998). A previous study (Ballesteros et al., 2008) conducted to investigate the effect of selective attention at encoding in normal aging and AD patients for familiar objects presented visually (Exp. 1) or haptically (Exp. 2) showed reliable priming in both young and older adults for objects that were attended at encoding but not for unattended objects, irrespective of the participant's age and the perceptual modality. AD patients did not show priming for attended objects, although previous studies showed implicit memory in AD patients under full attention at encoding (Ballesteros & Reales, 2004; Ballesteros et al., 2007; Fleischman, 2007).

Functional magnetic resonance (fMRI) studies of repetition priming when a fully attended stimulus was presented at encoding found reduced brain activation for repeated visual stimuli compared to new stimuli in brain areas that code for repeated stimulus properties (Schacter et al., 2007; Henson, 2003). Imaging studies conducted in young adults to investigate the effects of selective attention in brain activation occurring with stimulus repetition (Eger, Henson, Driver, & Dolan, 2004; Murray & Wojciulik, 2004; Vuilleumier, George, Lister, Armony, & Driver, 2005) have reported decreases in brain activation in the lateral occipital and

fusiform regions bilaterally, only for stimuli that were attended at study.

The lack of visual priming for attended pictures in adults with MCI in the present study mirror previous findings with AD patients (Ballesteros et al., 2008) and contrast with the normal priming obtained when AD patients attended to one stimulus at a time (Ballesteros & Reales, 2004; Ballesteros et al., 2007). In the present study, attended and unattended pictures appeared to the left or right of the fixation point of the computer screen. Adults with MCI did not show priming for attended pictures. The failure of selective attention at encoding places increased burdens on older adults with MCI. The lack of repetition priming for attended pictures when unattended ones are present at encoding might be a marker of pathological aging. This finding could be important because MCI could represent the early stages of AD (Burns & Zaudig, 2002; Morris et al., 2001) and it could be useful for preventing dementia. Carrying out stimulating activities such as physical exercise (Erickson & Kramer, 2009), cognitive training (Basak, Boot, Voss, & Kramer, 2008) and participation in social activities using new information computing technologies (Waterworth, Ballesteros, & Peter, 2009; Ballesteros, Peter, Waterworth, & Waterworth, 2012) might be beneficial (Hertzog, Kramer, Wilson, & Lindenberger, 2009). Further studies are required to confirm the efficiency of these activities in reducing the progression to AD (Peterson, 2011) and to associate the brain pathology with the impairment of specific attentional mechanisms and cognitive performance on repetition priming tasks.

To conclude, young adults outperformed older adults in all cognitive tasks, while adults with MCI performed significantly worse than healthy elders. Importantly, the two healthy groups showed similar levels of priming for stimuli attended at encoding. The lack of priming observed in the MCI group resembles findings from AD patients in visual and haptic priming tasks when selective attention was compromised at encoding. The lack of priming when attention is compromised at encoding might be a marker of pathological aging.

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