Age-Related Effects in Working Memory Recognition Modulated by Retroactive Interference

Elena Solesio-Jofre, Laura Lorenzo-López, Ricardo Gutiérrez, José María López-Frutos, José María Ruiz-Vargas, and Fernando Maestú

One of the main causes for age-related declines in working memory is a higher vulnerability to retroactive interference due to a reduced ability to suppress irrelevant information. However, the underlying neural correlates remain to be established. Magnetoencephalography was used to investigate differential neural patterns in young and older adults performing an interference-based memory task with two experimental conditions, interrupting and distracting, during successful recognition. Behaviorally, both types of retroactive interference significantly impaired accuracy at recognition more in older adults than in young adults with the latter exhibiting greater disruptions by interrupters. Magnetoencephalography revealed the presence of differential age-related neural patterns. Specifically, time-modulated activations in temporo-occipital and superior parietal regions were higher in young adults compared with older adults for the interrupting condition. These results suggest that age-related deficits in inhibitory mechanisms that increase vulnerability to retroactive interference may be associated with neural under-recruitments in a high-interference task.

THE increasing life expectancy occurred during the last decades demands the study of the particular needs of aged individuals (1); therefore, the study of age-related cognitive declines and their neural correlates is crucial. Aging is associated with memory impairments (2,3), particularly in working memory (WM). This theoretical construct involves the ability to retain and actively manipulate information temporarily. WM is a capacity-limited system, which affects both storage and processing, resulting in limited maintenance and attention capacity, respectively (4). WM supports other high-level cognitive processes, such as storage, rehearsal, and executive functions (5). Executive functions, in turn, include inhibitory mechanisms, necessary to delete task-irrelevant information and resolve interference during memory maintenance (6). Regarding the neural correlates of WM, neuroimaging research suggests that it represents an emergent property with neural interactions between the prefrontal cortex (PFC) and more posterior regions of the brain (7). Specifically, it seems that controlled top-down signals from the PFC modulate the storage in posterior parietal regions (8).

Inhibitory deficit hypothesis (9) provides a theoretical framework to understand which cognitive processes remain stable and which are affected by aging. Specifically, it postulates age-related difficulties to reduce interference from task-irrelevant information due to inefficient inhibitory control mechanisms (10,11). Age-related decrements in WM performance at recognition have been reported (12–16), especially in tasks in which subsequent events interfere with previous ones during the maintenance of information (17). This phenomenon, known as retroactive interference (RI), reduces the ability to suppress irrelevant information and also leads to declines in bottom-up mechanisms.

Two main sources of RI might affect inhibitory mechanisms, distractions, and interruptions. Distractions are referred to the irrelevant information that should be ignored and is related to top-down suppression signals from the PFC (18,19), whereas interruptions are referred to the information encountered as secondary and involve the reallocation of cognitive resources in order to reactivate disrupted representations, which is related to the medial temporal lobe (MTL) and the PFC (19,20). Distractions are defined by an

unintended attention shift, whereas interruptions could include an intended or an unintended attention shift with an additional task that might be performed. Recently, functional neuroimaging and neurophysiological tools have been employed to examine the neural substrates of these age-related memory impairments. Some experiments have found greater neural activations in older adults compared with young adults (21-23), whereas others have found the opposite results with under-recruitments in the elderly population (24,25). According to the inhibitory deficit theory, different authors have observed a progressive loss of frontal activity with aging (26,27), which may be precisely related to a difficulty to suppress irrelevant responses. Gazzaley and colleagues (28) provided further information by demonstrating age-related attention deficits circumscribed to the top-down suppression of irrelevant distractions with preserved enhancement of relevant information at early stages of visual processing. These heterogeneous results indicate that the relationship between brain function and age-related memory declines remains unclear. Note that most neuroimaging studies have explored age-related effects on distracting interference without directly addressing the impact of both distractions and interruptions in the elderly. However, a recent electroencephalographic study has revealed distinct neural mechanisms underlying the detrimental influence of both types of interference on WM in older adults (19). Focusing attention on early neural activity associated with visual stimulus representations and attentional control, these authors explained age-related declines by an excessive attentional allocation to distractors, although mechanisms for interruptions remain unclear. In summary, more research needs to be conducted in order to explore the impact of interruptions and distractions on recognition and, a central issue, the presence of age-related changes in the temporal dynamics of neural activity. In this regard, the present study explores age-related deficits in inhibitory mechanisms related to task-irrelevant suppression and also provides novel contributions by considering the brain as a holistic system in which different networks are characterized by specific temporal dynamics crucial to perform a task. This study used magnetoencephalography (MEG), which is an ideal noninvasive tool to explore the dynamic properties of the neural underpinnings of the age-related decline in WM. MEG directly measures, with optimal temporal resolution (ie, ms), brain magnetic fields from pyramidal neurons in the human cortex while the subject is performing a task. In contrast with previous studies that focused on early processing stages during encoding, we were interested in neural activity during WM recognition. Although it has been proposed that "pure" recognition processes are better preserved than encoding processes with normal aging (29,30), it has been demonstrated that successful retrieval of recently formed representations is strongly affected by interference (31), and older adults are disproportionally sensitive to interference in memory tasks (32). The current study thus aimed to examine age-related changes in brain activity during recognition after the presentation of two types of RI, interruptions and distractions. To explore age-related changes, as well as to assess differences in WM performance, two groups of individuals, young (19–35 years old) and older (56–75 years old) adults, performed a delayed paired-associate task for faces in which interruptions and distractions were presented during the maintenance stage; MEG was recorded throughout the task. We examined the temporal dynamics of brain magnetic activity during the first 1,000 ms after the onset of each correct response at recognition.

Based on the inhibitory deficit theory, we hypothesized that an age-related increased susceptibility to RI, due to a reduced ability to suppress irrelevant information, would be associated with neural changes in both interrupting and distracting conditions. Older adults would show under-recruitment and delayed activity within our 1,000-ms time window in posterior-frontal regions engaged in both earlier bottom-up and later top-down processes, respectively, compared with young adults. Suppression deficits would cause older adults to reach their WM capacity limit earlier by allowing irrelevant information to intrude and consume limited storage capacity and thus damage cognitive performance in our WM task.

MATERIALS AND METHODS

Participants

Twenty-eight young (mean age 23.04 years, SD of 4.85 years, range 19-35 years, 23 women) and twenty-three older adults (mean age 65.27 years, SD of 4.95 years, range 56-75 years, 17 women) participated in the study. All subjects were healthy, right-handed, and presented normal or correctedto-normal visual acuity. Subjects were assigned in two experimental conditions, interrupting and distracting. Fifteen young (mean age 24.20 years, SD of 5.51 years, range 19-35 years, 11 women) and 12 older adults (mean age 65.08, SD of 4.81 years, range 56-75 years, 9 women) were included in the interrupting condition, whereas 13 young (mean age 21.20 years, SD of 3.80 years, range 19–31 years, 12 women) and 11 older subjects (mean age 65.46 years, SD of 5.32 years, range 58-73 years, 8 women) were included in the distracting condition (see Table 1 for subjects' characteristics). Written informed consent was obtained for all subjects. The study was approved by the Institutional Review Board at University Complutense and was in accordance with the Declaration of Helsinki.

Tasks and Stimuli

Two auditory visual-adapted delayed paired-associate tasks corresponding to each experimental condition, interrupting and distracting, were employed. A "LEARN" yellow cue appeared for 500 ms indicating the beginning of each trial and was followed by a blank screen for 200 ms. Two paired associates, each of them composed of a visual

Table 1. Participants' Characteristics

	n	Age	Education	MMSE	rGDS
Interrupting condition $(n = 27)$					
Young	15	24.2 (5.51)	3.93 (0.27)	29.77 (0.44)	0.92 (1.38)
Older	12	65.08 (4.81)	3.08 (1.08)	29.17 (0.83)	1.58 (2.47)
Distracting condition $(n = 24)$					
Young	13	21.70 (3.80)	4.00 (0.00)	29.58 (0.67)	0.83 (1.03)
Older	11	65.46 (5.32)	3.00 (1.18)	29.55 (0.69)	0.91 (1.05)

Note: Education ratio from 1 to 4, 1 = 1-5 years, 2 = 6-8 years, 3 = 9-12 years, 4 = 13-17 years; MMSE = mini-mental state examination; rGDS = reduced geriatric depression scale; SD = standard deviation. Values are represented as mean (SD).

stimulus (face) plus an auditory stimulus (attribute describing some aspect of the face), were subsequently shown for 2,000 ms, interleaved with a 200-ms blank screen. Subjects were instructed to memorize those two paired associates presented (encoding stage). After a 500-ms blank screen, an interfering stimulus of a famous face was presented during 3,000 ms (maintenance stage). In the interrupting condition (see Figure 1A), participants were required to answer a yes or no question presented auditorily about the famous face by pressing one of two response buttons. By contrast, in the distracting condition (see Figure 1B), no question was asked, though participants were instructed to press a button in order to control potential group differences in motor components. A 500-ms blank screen followed. Next, a 500-ms "REMEMBER" signal in capital letters appeared, followed by a 200-ms blank screen. Thereafter, two paired associates were presented during 2,000 ms each, interleaved with a 200-ms blank screen. Finally, another blank screen appeared for 200 ms. Subjects were required to identify, by pressing a button, whether each paired associate had appeared during the initial encoding stage (recognition stage, Figure 1).

Visual stimuli consisted of 420 colored pictures of neutral-expression faces. Sex and age were controlled across pictures. Auditory stimuli were stereo recorded with a frequency of 44100 Hz and 16 bits. A noise reduction filter with auto spectral subtraction was applied, and stimuli were edited to have a duration of 2,000 ms. A total of 300 words were recorded as auditory stimuli: 100 were adjectives from the dictionary of the Royal Academy for the Spanish Language, 100 were professions, and 100 were places of residency. The last two categories were selected from a data set from the Spanish Institute of Statistics. Paired associates at encoding

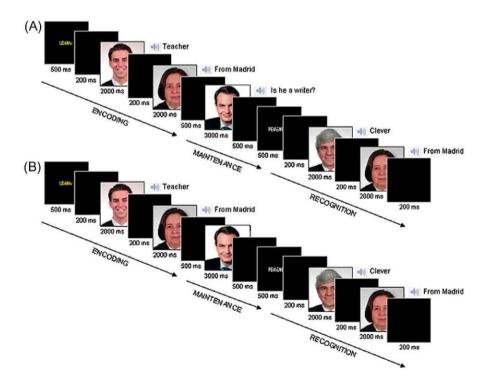


Figure 1. Trial structure in the interrupting condition (A) and distracting condition (B). Two paired associates to memorize were shown subsequently at encoding. An interfering picture of a famous face was displayed at maintenance stage with a difference in the instructions given to participants in each experimental condition. In the interrupting condition, they were asked about some attributes related to that picture, whereas in the distracting condition, no question was asked. Two more paired associates were shown subsequently at recognition and participants reported whether each of them matched up with those previously encoded.

and interfering faces at maintenance, 240 and 120 stimuli, respectively, were novel across all trials. For the overall probes (240), half matched a cue stimulus, whereas the other half did not. For the latter, 60 of the 120 probes consisted of a cue visual stimulus plus a novel auditory attribute and the 60 remaining consisted of a novel visual stimulus plus a cue auditory attribute.

Procedures

MEG scans were recorded during the performance of the delayed paired-associate task. Due to the great number of trials necessary for a high signal-to-noise ratio with MEG recordings, it was unfeasible to develop a within-subjects design with both types of RI as the within-subjects factor. We developed a between-subjects design very suitable to avoid fatigue or practice effects instead. Some of the variables that might contaminate between-subjects designs and reduce their power were carefully controlled, such as sample size, individual variability (eg, age, nationality, education, psychological traits), or environmental factors (eg, time of the day participants were tested).

One task per experimental condition was programmed using E-Prime software (Psychology Software Tools, Inc.). Each task was composed of 120 trials and was presented in two blocks of 15 minutes each, separated by a 2-minute resting interval.

Prior to MEG scans, participants undertook a 20-trial training session. They were instructed to respond with a button press as quick and accurate as possible. Button assignment was counterbalanced across participants in each condition.

Images subtended 1.8° horizontally and 3° vertically of visual angle at a 60-cm viewing distance and were centered at the fovea. They were projected through an LCD video-projector (Sony VPL-X600E) situated outside the shielded room onto a series of in-room mirrors.

Neural Data Acquisition and Preprocessing

Neuromagnetic fields were recorded, within a shielded room, with a 148-channel whole-head magnetometer array (Magnes 2500 WH; 4-D Neuroimaging, San Diego, CA) at a sampling rate of 678.17 Hz and a band-pass online filter between 0.1 and 100 Hz. MEG data were submitted to an interactive noise reduction procedure that aided in reducing environmental noise part of the signal analysis package. The electro-oculogram signals were acquired through a Synamps amplifier (Neuroscan, EL Paso, TX) by placing two electrodes near the left and right outer canthus and two above and below the right eye.

We selected an epoch length of 1,000 ms starting after the onset of each probe stimulus during the recognition stage. Initially, MEG data were baseline corrected on the basis of a pre-stimulus 100 ms time window. Thereafter, the signal was low-pass filtered at 20 Hz. Epochs contaminated by ocular artifacts were off-line corrected by means of BESA

artifact-correction tool version 5.1.8 (MEGIS Software GmbH, Gräfelfing, Germany). Data were then visually inspected for movement artifacts, and epochs with peak-to-peak amplitudes exceeding a threshold of 3 pT were discarded from further analysis. Thereafter, the surviving single-trial event-related magnetic fields (ERMFs) were then averaged together selectively in each experimental condition (interrupting condition and distracting condition) and computed only for those trials with correct responses (hits and correct rejections) at the recognition stage. Both age groups exhibited a similar number of trials per condition that survived this criterion. Hence, the potential effect that differences in the number of trials could have on the power and reliability of posterior source estimates was controlled. Although of interest, it was not possible to compute MEG averages for unsuccessful recognition because a minimum of 90 epochs was not achieved.

Neural Data Analysis

In order to estimate the cortical origin of the ERMFs, we conducted source reconstruction data analyses. Specifically, an 12-minimum norm estimation procedure (33) was employed. The minimum norm solution provides a straightforward solution to the inverse problem and is a very suitable method whenever no reliable a priori information about source generators is available, for instance, when complex cognitive tasks are employed (32), such as our interferencebased WM task. The Tikhonov regularization was applied, using the Brainstorm open source Matlab toolbox (http:// neurimage.usc.edu/brainstorm/). The Montreal Neurological Institute phantom brain (34), implemented in SPM5 (http:// www.fil.ion.ucl.ac.uk/spm/software/spm5/), with 7204 surface dipoles served as brain model to estimate the current source distribution. This Montreal Neurological Institute dipole mesh (7204 nodes) was used to calculate the forward solution using a head model based on overlapping spheres. The underlying current source density of the ERMFs, that is the source strength at each node of the Montreal Neurological Institute phantom brain, was estimated for each experimental condition (interrupting and distracting) and age group (young and older adults).

Behavioral Statistical Analyses

Two measures were calculated in order to analyze behavioral performance at recognition: mean reaction times for correct responses (hits and correct rejections) and percentage of correct responses. Comparisons between age groups within each experimental condition were subjected to a one-way analysis of variance with age (young and older adults) as between-subjects factor.

Neural Statistical Analysis

MEG data were subjected to a nonparametric cluster–based permutation test to explore possible differences in brain

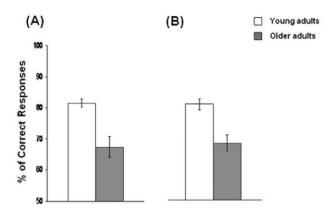


Figure 2. Participants' performance at recognition. Young adults showed a greater accuracy compared with older subjects in the interrupting condition (A) and distracting condition (B). Error bars indicate standard error of the mean.

activity (MATLAB; MathWorks, Natick, MA). This test effectively controls the family-wise error rate in a situation involving multiple comparisons (7204 nodes and 746 time-points) by clustering neighboring points that exhibit the same effect in time and space, considering each point as a (sensor and time-point) pair. We conducted comparisons between age groups (young and older adults) with experimental condition (interrupting and distracting) as between-subjects factor. Nine hundred permutations were computed and minimum norm estimation source strength values calculated per individual across time were shuffled within each condition under the null hypothesis of no differences between age groups (35).

At a primary threshold level, two-sample t tests were performed for each of the 7,204 nodes at a 0.05 (uncorrected) significance level. We selected all nodes significant larger than this primary threshold for subsequent cluster analysis based on spatio-temporal adjacency criteria. At a suprathreshold level, we calculated the so-called exceedance mass of the largest cluster (36), defined as the sum of those significant t values within a cluster. The largest clusters were precisely those with the highest exceedance mass. For each cluster, the p value was approximated by the Monte Carlo estimate (35,37).

RESULTS

Behavioral Performance

A significant effect of age was observed on the percentage of correct responses for the interrupting condition, F(1,26) = 17.368, p < .0001; young: $81.44 \pm 5.11\%$; older: $67.43 \pm 11.75\%$, and the distracting condition, F(1,23) = 15.991, p < .001; young: $87.62 \pm 7.65\%$; older: $72.42 \pm 10.92\%$, indicating that young adults performed the recognition memory task more accurately than older adults in both experimental conditions (see Figure 2A and B). However, there were no significant effects of age on mean reaction times either for the interrupting, F(1,26) = 1.058, p < .314; young: 610.20 ± 139.92 ms; older: 665.17 ± 135.53 ms, or

the distracting condition, F(1,23) = 0.182, p < .674; young: 573.54 ± 78.17 ms; older: 587.09 ± 76.89 ms (Figure 2).

Altogether, our behavioral analyses indicated that young adults were more accurate than older adults in both interference conditions. Based on these observations, we compared the distributed source localization of brain magnetic activity (ERMFs) between both age groups.

ERMFs during Successful Recognition: Comparisons Between Young and Older Adults

In this section, we summarize the main results regarding those brain magnetic differences between young and older adults within each experimental condition. We took the largest cluster-level statistics under the following criterion: for 900 permutations, the 95th percentile is at $900 \times 0.05 = 45$ (c), so the critical primary threshold was the 46th (c + 1) largest member of the permutation distribution (38).

For the interrupting condition, this primary threshold was 0.77×10^5 . Our cluster-based permutation test revealed the presence of one significant cluster in favor of young adults with a Monte Carlo p value of .022.

For the distracting condition, the critical threshold was 0.93×10^5 . No significant clusters were obtained for one or the other age group. In fact, the cluster closest to significance in favor of young adults had a corresponding Monte Carlo p value of .505.

These results reflect the presence of differential neural patterns at recognition with higher activations in young compared with old adults after the presentation of interruptions, whereas no group differences were observed after the presentation of distractions. The specific spatio-temporal dynamics of this significant activity in young adults for the interrupting condition are the following: activity was firstly observed in the right superior parietal lobe including the precuneus (Brodmann areas 5/7) and the right inferior and medial temporal cortices, including the fusiform gyrus (Brodmann areas 22/37), during the 438–550 ms time window. Statistical differences between age groups in temporal lobe activity disappeared at approximately 550 ms, whereas significant differences in the superior parietal cortex were present up to 814 ms. The nonparametric maps for age group differences in the interrupting condition are depicted in Figure 3.

DISCUSSION

The present study examined the neural changes underlying the decline in WM, particularly in inhibitory mechanisms, that accompanies aging and the neural modulation by two types of RI, interruptions and distractions, during successful recognition. Our behavioral investigation of age-related differences in performance at recognition revealed a greater accuracy in young adults compared with older adults in both interrupting and distracting conditions. This finding suggests that the presentation of two types of interference

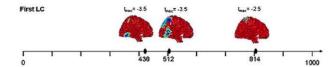


Figure 3. Statistical maps referred to cortical source largest clusters (LC) indicating significant higher activity for the young adults group relative to the older adults group in the interrupting condition. Only statistical differences are shown considering the corresponding minimum Monte Carlo p value (in text). A time axis (in milliseconds) is included to remark the temporal dynamics of neural differences.

during the maintenance of information leads to age-related deficits in the ability to suppress irrelevant information and to correctly recognize two previous encoded paired associates, which is consistent with previous studies (39,40). The absence of significant effects on reaction times could have two potential origins. One plausible explanation might be that both young and older participants could be equally affected by distractions and interruptions with long reaction times. Second, a possible methodological rationale might be related to the sample size and statistical power. However, both of them remain speculative and further experiments with a greater sample size should be conducted in order to clarify it.

MEG results indicated the presence of age-related differential spatio-temporal patterns of neural activity during successful recognition. Specifically, young adults showed higher time-modulated activity in temporo-occipital and parietal areas for the interrupting condition, whereas no statistical differences were observed for the distracting condition.

Age-Related Changes in Neural Patterns at Recognition as a Consequence of Retroactive Interference

Multiple brain structures including medial temporal (41), precentral, and superior parietal areas (42) have been associated with interference resolution processes something in accordance with our results. However, one of the main contributions of the present study is the description of the temporal dynamics regarding neural activity. In this regard, we obtained differential greater activity in favor of young participants for the interrupting condition over the right temporo-occipital cortices, including medial, inferior temporal areas, and the fusiform gyrus at medium latencies, and right superior parietal areas at medium and late latencies.

The absence of between-group differences in the interrupting condition at early sensory stages may indicate that primary sensory processing is not affected by RI (43,44). However, we obtained higher neural patterns at postsensorial stages, particularly at medium and late latencies. In general, temporo-occipital areas belong to a visual pathway that includes face-selective regions, such as the fusiform gyrus and involves face perception (45–47). Our results may indicate that the mediation of the occipital gyrus at medium latencies is necessary for the basic analysis of facial features that allows the fusiform gyrus to identify a photograph of a face (48). Higher activations in young participants in the

MTL at medium latencies may be related to interference resolution. Specifically, in order to bring the encoded information back from the off-line to the online state, the same areas as for encoding were reactivated at retrieval after the presentation of an interfering stimulus during maintenance (6,20,49). When the online maintenance is interrupted by external interference, it is temporarily deactivated until a recognition judgment reactivates again the to-be-retrieved information. The MTL is engaged in reactivation processes at retrieval from long-term memory and WM as well.

In this regard, our interrupting task constitutes a high-demanding task, in which the online maintenance of paired associates presented at encoding is interrupted at maintenance by the additional necessity to access long-term stores in order to explicitly retrieve information from episodic memory to correctly answer a yes or no question. This factor might have a direct impact on WM recognition, by interfering retroactively with those paired associates presented at encoding and altering their memory traces. Thus, reactivation processes at recognition are crucial in this high-demanding task in order to override RI.

As previously mentioned, MEG results also revealed significant higher recruitments of superior parietal areas at medium and late latencies in young adults relative to older adults in the interrupting condition. Despite traditional theories emphasizing parietal contributions to spatial attention and sensorio-motor integration (50), significant parietal lobe activation has been also observed in previous event-related potentials (51,52) and functional neuroimaging studies during the performance of memory retrieval tasks (53–58). Our greater activated network including the precuneus, medial, and lateral parietal cortex may be associated with the correct recognition of information (17,59,60); particularly, these regions may subserve temporal structures in order to resolve external interference and accomplish a successful recognition judgment.

Literature in cognitive aging describes age-related neural under-recruitments as one key element associated with cognitive decline (24). In the present study, age-related underrecruitments for the interrupting condition were associated with detriments in accuracy, indicating that such neural under-recruitments are accompanied by WM difficulties. Specifically, under-recruitments in occipital areas at medium latencies may reflect bottom-up impairments at postperceptual stages as a consequence of interference. One mechanism explaining MTL under-recruitments may be the presence of age-related reduced abilities to reactivate the memoranda stored off-line after the presentation of interrupting interference (19) in order to bring it back to the online state. In this regard, both the PFC and MTL have been shown to send signals to posterior association areas in the postinterruption period (19,61,62). Specifically, Sakai and colleagues (20) suggested a double dissociation between the MTL and PFC by manipulating the reactivation of maintained information and the demand for interference resolution. It seems that the MTL is engaged in the reactivation of the information stored off-line, whereas the PFC has a primary function in the topdown selection of task-relevant information to override interference. According to our results reflecting age-related under-recruitments in the MTL with the absence of PFC differences, we suggest that age-related WM declines after interruptions may be related to a difficulty to reactivate the off-line information. This may be related to deficits in the suppression of prepotent responses rather than deficits in the selection of task-relevant information. Older individuals may fail to delete the interrupting information from WM, which retroactively interferes with subsequent memory decisions at recognition (63). Additionally, it has been established that the disruption of medial temporal projections to medial parietal reflects a loss of functional inhibition not only in normal aging but also in Alzheimer's disease (64), which may explain our age-related under-recruitments in parietal structures at medium and late latencies in terms of inhibitory deficits.

Hence, we suggest that age-related diminished neural activity may be related to deficits in earlier postsensorial and later top-down processes. It may be indicative of inefficient inhibitory mechanisms to suppress irrelevant stimuli, responsible for an increased vulnerability to RI, which leads to difficulties to reactivate and correctly recognize paired associates during retrieval. These findings are consistent with behavioral (9) and neuroimaging research in cognitive aging (27) showing reduced occipital, temporal, and parietal activities in older adults at recognition (23,51,65–67).

Finally, we would like to emphasize that our focus of interest was to explore age-related neural differences in the presence of RI. We did not include a noninterference condition in order to maximize power to investigate group differences in our two interference conditions.

To summarize, the current study importantly contributes to the notion that aging impairs WM ability, particularly inhibitory mechanisms that increase vulnerability to RI. We also provide novel evidence about the brain temporal dynamics and show the neural substrates of reported behavioral changes during successful recognition.

Our findings extend previous research by reflecting agerelated neural under-recruitments in temporo-occipital areas at medium latencies and superior parietal areas at medium and later latencies after the presentation of interrupting interference, whereas no neural changes were observed after the presentation of distracting interference, which suggests that aging affects both earlier postsensorial and later topdown mechanisms in a high interfering task. These results may indicate the presence of age-related inhibitory deficits to suppress irrelevant information leading to difficulties to reactivate the off-line representations to the online state and correctly make a recognition judgment. These results have direct implications to better understand the functioning of the aged brain and may help to improve the quality of life of elderly by training inhibitory mechanisms in order to imrove resistance to RI.

FUNDING

This work was supported by the Spanish Ministry of Education and Science (grant AP2005-0332); La Xunta de Galicia:Ángeles Alvariño Program; and the Spanish Ministry of Science and Innovation (grant BES-2007-15773, SEJ2006-07560).

Conflict of Interest

All authors declare no conflict of interest.

ACKNOWLEDGMENT

The authors thank Drs. Stephan Moratti and Nazareth P. Castellanos for technical support.

Fielding RA, Rejeski WJ, Blair S, et al. The lifestyle interventions and independence for elders study: design and methods. *J Gerontol A Biol Sci Med Sci*. 2011;66A(11):1226–1237. doi:10.1093/gerona/glr123.

Baune BT, Roesler A, Knecht S, Berger K. Single and combined effects of cerebral white matter lesions and lacunar infarctions on cognitive function in an elderly population. *J Gerontol A Biol Sci Med Sci.* 2009;64(1):118–124.

Gmehlin D, Kreisel SH, Bachmann S, Weisbrod M, Thomas C. Age effects on preattentive and early attentive auditory processing of redundant stimuli: is sensory gating affected by physiological aging? *J Gerontol A Biol Sci Med Sci.* 2011;66(10):1043–1053. doi: 10.1093/gerona/glr067.

Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav Brain Sci.* 2001;24:87–185. Miyake A, Shah P. Toward unified theories of working memory. Emerging general consensus, unresolved theoretical issues, and future research directions. In: Miyake A, Shah P, eds. *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control.* New York: Cambridge University Press; 1999:102–134.

Sakai K. Reactivation of memory: role of medial temporal lobe and prefrontal cortex. *Rev Neurosci.* 2003;14:241–252.

D'Esposito M. From cognitive to neural models of working memory. *Philos Trans R Soc of Lond B Biol Sci.* 2007;29:761–772.

Halford GS, Cowan N, Andrews G. Separating cognitive capacity from knowledge: a new hypothesis. *Trends Cogn Sci.* 2007;11:236–242.

Hasher L, Zacks RT. Working memory, comprehension, and aging: a review and a new view. In: Bower GH, ed. *The Psychology of Learning and Motivation*. New York: Academic Press; 1988:193–225.

May CP, Zacks RT, Hasher L, Multhaup KS. Inhibition in the processing of garden-path sentences. *Psychol Aging*. 1999;14:304–313.

Zacks RT, Hashe L, Li KZH. Human memory. In: Craik FIM, Salthouse TA, eds. *The Handbook of Aging and Cognition*. Mahwah, NJ: Erlbaum; 1999:200–230.

Cowan N. What are the differences between long-term, short-term, and working memory? *Prog Brain Res.* 2008;169:323–338.

Grady CL. Functional brain imaging and age-related changes in cognition. *Biol Psychol*. 2000;54:259–281.

Hedden T, Park D. Aging and interference in verbal working memory. *Psychol Aging*. 2001;16:666–681.

Lewandowsky S, Duncan M, Brown GDA. Time does not cause forgetting in short-term serial recall. *Psychol Bull Rev.* 2004;11: 771–700

Salthouse TA, Babcock RL, Shaw RJ. Effects of adult age on structural and operational capacities in working memory. *Psychol Aging*. 1991; 6:118–127.

Buckner RL, Wheeler ME. The cognitive neuroscience of remembering. *Nat Rev Neurosci.* 2001;2:624–634.

Chao LL, Knight R. Contribution of human prefrontal cortex to delay performance. *J Cog Neurosci*. 1998;10:167–177.

Clapp WC, Gazzaley A. Distinct mechanisms for the impact of distraction and interruption on working memory in aging. *Neurobiol Aging*. In press. doi:10.1016/j.neurobiolaging.2010.01.012.

Sakai K, Passingham RE. Prefrontal selection and medial temporal lobe reactivation in retrieval of short-term verbal information. *Cereb Cortex*. 2004;14:914–921.

Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000;12:1–47.

Grady CL, Bernstein LJ, Beig S, Siegenthaler L. The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. *Psychol Aging*. 2002;17:7–23.

Morcom AM, Rugg MD. Effects of age on retrieval cue processing as revealed by ERPs. *Neuropsychologia*. 2004;42:1525–1542.

Logan JM, Sanders AL, Snyder AZ, Buckner RL. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*. 2002;33:827–840.

Stebbins GT, Carrillo MC, Dorfman J, et al. Aging effects on memory encoding in the frontal lobes. *Psychol Aging*. 2002;17:44–55.

Garavan H, Ross TJ, Li SJ, Stein EA. A parametric manipulation of central executive functioning. *Cereb Cortex*. 2000;10:585–592.

Jonides J, Marshuetz C, Smith EE, et al. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. *J Cogn Neurosci*. 2000;12:188–196.

Gazzaley A, Cooney JW, Rissman J, D'Esposito M. Top-down suppression deficit underlies working memory impairment in normal aging. *Nat Neurosci*. 2005;8:1298–1300.

Anderson ND, Craik FI, Naveh-Benjamin M. The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs. *Psychol Aging*. 1998;13:405–423.

Craik FI, Govoni R, Naveh-Benjamin M, Anderson ND. The effects of divided attention on encoding and retrieval processes in human memory. *J Exp Psychol Gen.* 1996;125:159–180.

Anderson MC, Neely JH. Interference and inhibition in memory retrieval. In: Bjork EL, Bjork RA, eds. *Memory: Handbook of Perception and Cognition*. (2nd ed.). San Diego, CA: Academic Press; 1996: 237–313

Hämäläinen MS, Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. *Med Biol Eng Comput*. 1994;32:35–42. Hauk O. Keep it simple: a case for using classical minimum norm estimation in the analysis of EEG and MEG data. *Neuroimage*. 2004; 21:1612–1621.

Collins DL, Zijdenbos AP, Kollokian V, et al. Design and construction of a realistic digital brain phantom. *IEEE Trans Med Imaging*. 1998; 17:463–468.

Ernst MJ. Permutation methods: a basis for exact inference. *Stat Sci.* 2004;19:676–685.

Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage*, 1997:5:83–96.

Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods*. 2007;1:177–190.

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp.* 2001;15:

Grady CL, Craik FI. Changes in memory processing with age. *Curr Opin Neurobiol*. 2000;10:224–231.

Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. *Curr Opin Neurobiol.* 2005;15:245–251.

Öztekin I, Curtis CE, McElree B. The medial temporal lobe and the left inferior prefrontal cortex jointly support interference resolution in verbal working memory. *J Cogn Neurosci*. 2009;21:1967–1979.

Leung HC, Zhang JX. Interference resolution in spatial working memory. *Neuroimage*. 2004;23:1013–1019.

Rousselet GA, Husk JS, Pernet CR, et al. Age-related delay in information accrual for faces: evidence from a parametric, single-trial EEG approach, B.M.C. *Neuroscience*. 2009;10:114.

Wiese H, Schweinberger SR, Hansen K. The age of the beholder: ERP evidence of an own-age bias in face memory. *Neuropsychologia*. 2008;46:2973–2985.

Druzgal TJ, D'Esposito M. Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *J Cogn Neurosci*. 2003;15:771–784.

Ranganath C, Cohen MX, Dam C, D'Esposito M. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *J Neurosci.* 2004; 24:3917–3925.

Ranganath C, DeGutis J, D'Esposito M. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Brain Res Cogn Brain Res*. 2004;20:37–45.

Haxby JV, Petit L, Ungerleider LG, Courtney SM. Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage*. 2000;11:145–156.

Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E. Activation of medial temporal structures during episodic memory retrieval. *Nature*. 1996;380:715–717.

Mesulam MM. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci.* 1999;354:1325–1346.

Ally BA, Simons JS, McKeever JD, Peers PV, Budson AE. Parietal contributions to recollection: electrophysiological evidence from aging and patients with parietal lesions. *Neuropsychologia*. 2008;46:1800–1812. Rugg MD, Curran T. Event-related potentials and recognition memory. *Trends Cogn Sci.* 2007;11:251–257.

Cabeza R, Nyberg L. Imaging cognition: an empirical review of PET studies with normal subjects. *J Cogn Neurosci*. 1997;9:1–26.

Hamidi M, Tononi G, Postle BR. Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation. *Brain Res.* 2008;1230:202–210.

Postle BR, D'Esposito M. "What"-Then-Where" in visual working memory: an event-related fMRI study. *J Cogn Neurosci*. 1999;11: 585–597

Rugg MD, Otten LJ, Henson RN. The neural basis of episodic memory: evidence from functional neuroimaging. *Philos Trans R Soc Lond B Biol Sci.* 2002;357:1097–1110.

Vincent JL, Snyder AZ, Fox MD, et al. Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J Neurophysiol*. 2006;96:3517–3531.

Wagner AD, Shannon BJ, Kahn I, Buckner RL. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci.* 2005;9:445–453.

Simons JS, Peers PV, Hwang DY, et al. Is the parietal lobe necessary for recollection in humans? *Neuropsychologia*. 2008;46:1185–1191.

Velanova K, Lustig C, Jacoby LL, Buckner RL. Evidence for frontally mediated controlled processing differences in older adults. *Cereb Cortex*. 2007;17:1033–1046.

Naya Y, Yoshida M, Miyashita Y. Backward spreading of memory-retrieval signal in the primate temporal cortex. *Science*. 2001;291: 661–664.

Tomita H, Ohbayashi M, Nakahara K, Hasegawa I, Miyashita Y. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature*. 1999;14:699–703.

Hasher L, Zacks RT, Rahhal TA. Timing, instructions, and inhibitory control: some missing factors in the age and memory debate. *Gerontology*. 1999;45:355–357.

Daselaar SM, Fleck MS, Dobbins IG, Madden DJ, Cabeza R. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cereb Cortex*. 2006;16:1771–1782.

Fjell AM, Walhovd KB, Reinvang I. Age-differences in verbal recognition memory revealed by ERP. *Clin EEG Neurosci.* 2005;36:176–187. Joyce CA, Paller KA, McIsaac HK, Kutas M. Memory changes with normal aging: behavioral and electrophysiological measures. *Psychophysiology.* 1998;35:669–678.

Rugg MD, Mark RE, Gilchrist J, Roberts RC. ERP repetition effects in indirect and direct tasks: effects of age and interitem lag. *Psychophysiology*. 1997;34:572–586.