Early Prefrontal Activation As a Mechanism to Prevent Forgetting in the Context of Interference

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Objective: *Recent research has focused on interference resolution deficits as the main cause of short-term memory decreases in aging. To determine whether activation of brain compensatory mechanisms occur during the encoding process in older people. Moreover, two different levels of interference (distraction and interruption) were presented during the maintenance period to examine how they modulate brain activity profiles.* **Design:** *A delayed match-to-sample task with two experimental conditions: distraction and interruption.* **Participants:** *Twenty-seven young adults from Complutense University of Madrid and 20 healthy older adults from Complutense Elderly University of Madrid.* **Measurements:** *Magnetoencephalography scans were recorded during the execution of a working memory interference task. Brain activity sources from younger and older adults during the encoding stage were compared in each condition using minimum norm estimation analyses.* **Results:** *The elderly showed enhancement of prefrontal activity during early latencies of the encoding process in both conditions. In the distraction condition, enhanced activity was located in left ventro-lateral prefrontal regions, whereas in the interruption condition, enhanced activity was observed in the right ventral prefrontal areas and anterior cingulate cortex.* **Conclusion:** *Increased recruitment of prefrontal regions in the elderly might be related to the processing depth of information, encoding of new information and semantic associations that are successfully recalled, and with interference resolution and prepa-ratory control when the level of interference becomes higher. These prefrontal modu-lations during early latencies might reflect a higher top-down control of the encoding process in normal aging to prevent forgetting.* (Am J Geriatr Psychiatry 2013; 21:580–588)

Key Words: Aging, inhibition, interference, magnetoencephalography, top-down control, working memory

Recent theories about memory and forgetting have changed the focus from the mere time decay to the influence of interference as the main cause of information lost, specially in short-term memory.[1] Simultaneously, the concept of cognitive inhibition has received growing attention due to its experimentally observed role in the successful management of mental processes.[2] Hasher and Zacks[3] have proposed a working memory (WM) capacity model with access, deletion, and restraint as key processes. In their model, cognitive inhibition is central for the efficient operation of each process of WM. When inhibitory mechanisms are normally functioning, they limit the entrance of nonrelevant information. This nonrelevant information works as interference for outstanding information to the task goal if inhibitory mechanisms are not properly functioning due to the limited capacity of WM. Therefore, all of those processes require inhibitory mechanisms for their adequate functioning.[3] Furthermore, this framework emphasizes individual differences in the ability of overriding interfering information during WM performance. Thus, this perspective results to be of interest for the investigation of aging and WM. It is well known that the elderly show decreased WM performance.[4–6] They do not seem to show pure maintenance deficits,[7] but in contrast, they exhibit interference resolution difficulties in WM tasks.[3,8,9]

Within the inhibitory framework, several studies have been published aimed at unraveling the neural mechanisms underlying the decrease in WM capacity observed in healthy elderly subjects, albeit with some discrepancies both in the experimental results and in their functional interpretation.[9] A consistent finding in many neuroimaging studies has been that healthy elderly people show increased cortical activity when compared with young subjects.[10–13] The prefrontal cortex (PFC) has been identified to be more involved in successful memory performance with increasing age, probably as a consequence of structural and functional age–related changes.[9,14–16]

Classical memory theories have proposed that encoding is crucial for successful retrieval highlighting the importance of accurate encoding for proper recalling of the information encoded before.[17,18] Some studies have shown age-related enhanced activity over prefrontal areas during the encoding stage for different WM tasks. Schiavetto et al.[19] reported enhancement of regional cerebral blood flow in the elderly during perceptual encoding in an object identity and location memory task. Rosen et al.[16] compared brain activity for younger and older people using functional magnetic resonance imaging while performing semantic and nonsemantic encoding of words and reported increased right prefrontal activity in elderly subjects with high memory scores relative to that of younger participants.

Whereas the effect of age on brain activity in WM has received some attention, less is known about how the aging brain handles interfering and irrelevant inputs. The aim of this study was to examine whether the presentation of stimuli corresponding to two levels of interference during the maintenance period modulates brain activity at the encoding stage reflecting different executive strategies for encoding, and if so, whether these modulations change with normal aging. Some studies have shown that distraction and interruption not only lead to different WM performance but also have measurable effects on neural activity when presented during the maintenance period.[20] In this study, interference has been considered to be the main cause of information loss in short-term memory. Therefore, to design experimental conditions as perceptually similar as possible, an auditory-visual WM task including two kinds of interferences during the maintenance stage was performed by young and healthy elderly participants. Distraction and interruption were expected to activate different executive strategies during the encoding stage. Furthermore, given the executive impairments reported in normal aging,[21–25] we expected not only a difference in WM performance level between the young and the elderly but also differences in neural activity in prefrontal areas during the encoding stage, which might be modulated by the level of interference at the maintenance stage (activating different strategies for encoding).

Neuroimaging techniques based on hemodynamic responses such as positron emission tomography, single photon emission computed tomography, or functional magnetic resonance imaging are very powerful tools because of their high spatial resolution. However, because of their low temporal resolution, their ability to isolate different processes during the time course of a WM task is limited. Little is known about the time course of the aforementioned increased PFC activity in the elderly during WM encoding in interference conditions.

Therefore, the aim of this study was to characterize age-related differences in the spatiotemporal patterns of brain activity underlying memory control during the encoding stage in the context of an interference paradigm. Magnetoencephalography (MEG) recordings benefit from an excellent temporal resolution in the millisecond range and good spatial resolution.[26] The spatiotemporal activity patterns were derived from MEG recording. On the basis of previous studies,[9,14–16] we hypothesized that elderly subjects would show stronger activation of frontal brain regions than younger subjects. We also expected these differential profiles to be modulated by the level of interference with additional prefrontal areas recruited during interruption, in which highest executive control would be needed to resist against highest level of interference. This kind of over-recruitment might be interpreted as a compensatory mechanism for the low resistance of the memory networks to interference.

MATERIALS AND METHODS

Participants

The sample consisted of 27 younger adults (22 women and 5 men, age range 19–35 years) and 20 older adults (14 women and 6 men, age range 56–76 years). Younger participants were recruited at Complutense University of Madrid and older participants were recruited at Complutense Elderly University of Madrid, where they were engaged in a program of university studies for the elderly.

All participants were healthy, right-handed, native Spanish speakers with normal or corrected-to-normal visual acuity. They all completed the Spanish version of the Mini-Mental State Examination (MMSE), the Reduced Geriatric Depression Scale (rGDS), and a semi-structured interview to discard any neurologic or psychiatric disease (MMSE score >27 and rGDS score <5).

Two experimental conditions were included in the study: distraction condition (DC) and interruption condition (IC). Twelve younger and 9 older adults took part in the DC experiment, whereas 15 younger and 11 older adults took part in the IC experiment. Age groups did not differ in level of education and MMSE and rGDS scores both for DC and IC (see Table 1 for demographic information).

Stimuli

Different kinds of stimuli were designed for each stage of the task. Items at the encoding stage were auditory-visual *paired associates* consisting of a photograph of the face of an anonymous person and an auditory word describing some attribute of the person (job, place of origin, or a qualifying adjective). For each of the distracting stimuli, a face of a Spanish celebrity or a very well-known non-Spaniard was used. The interrupting stimuli consisted of an additional auditory "yes/no" question about the celebrity. Finally, items at the recognition stage were designed in the same way as encoding items.

Images were projected through an LCD video projector (SONY VPL-X600E, Sony Electronics Inc., San Diego, CA) located outside the shielded room onto a series of in-room mirrors, the last of which was suspended approximately 60 cm above the participant's face. The visual angle subtended by the photographs was 1.8 degrees horizontally and 3 degrees vertically.

Words were presented acoustically through a pair of plastic air tubes and headphones, with the volume level individually adjusted before the task.

Task

Participants were subjected to an auditory-visual delayed match-to-sample task with two experimental conditions (DC and IC). E-PRIME 1.2 software (Psychology Software Tools, Inc. Sharpsburg, PA) was used for stimulus presentation. Under the assumption of interference as the main cause of information loss in short-term memory, distraction and interruption were used to allow the study the impact of different levels of interference in executive strategies for encoding while ensuring that both experimental conditions were as similar as possible perceptually.

Both conditions comprised 120 trials. Each trial began with a "LEARN" yellow cue shown for 500 milliseconds, followed by a 200-millisecond blank screen. Next, two encoding items appeared for 2,000 milliseconds each, interleaved with another 200-millisecond blank screen. Participants were instructed to memorize each pair (encoding phase). After another 200-millisecond blank screen, an interfering stimulus was displayed for 3,000 milliseconds. The IC participants had to answer a question about the

TABLE 1. Participants' Characteristics

	Distraction Condition				
	Age	Education Level	MMSE	rGDS	Gender (M/F)
YA, mean (SD)	21.17 (3.35)	4.00 (0.00)	29.66 (0.65)	0.75 (1.05)	1/11
OA, mean (SD)	65.00 (5.70)	3.77 (0.44)	29.55 (0.72)	0.88 (1.05)	2/7
Mann-Whitney *U*	0.00	48.00	49.50	48.00	46.50
Significance	p <0.0001	p = 0.702	p = 0.754	p = 0.702	p = 0.602
	Interruption Condition				
	Age	Education Level	MMSE	rGDS	Gender (M/F)
YA, mean (SD)	24.20 (5.50)	3.93 (0.25)	29.76 (0.43)	0.92 (1.38)	4/11
OA, mean (SD)	65.00 (5.03)	3.88 (0.33)	29.18 (0.87)	1.63 (2.57)	3/8
Mann-Whitney *U*	0.00	75.00	72.50	70.50	82.000
Significance	p <0.0001	p = 0.721	p = 0.610	p = 0.540	p = 1.000

Notes: An exact (permutation based) Mann-Whitney test was used. YA: younger adults; OA: older adults; M/F: male/female. Education level—1: basic studies; 2: primary studies; 3: secondary studies; 4: superior studies.

celebrity face by pressing one of two response buttons, whereas no questions were asked from the DC participants. However, participants were instructed to make a button response in order to discard potential group differences due to a motor component (maintenance phase). Next, after yet another 200-millisecond blank screen, a "REMEMBER" white cue appeared for 500 milliseconds, followed by another 200-millisecond blank screen. Thereafter, two recognition items were shown during 2,000 milliseconds each, also interleaved with a 200-millisecond blank screen. Finally, another blank screen appeared for 200 milliseconds. Subjects were required to report with a button press whether each paired associate had appeared during the encoding phase (recognition phase) (Figure 1). Response button assignment was counterbalanced across participants in both conditions.
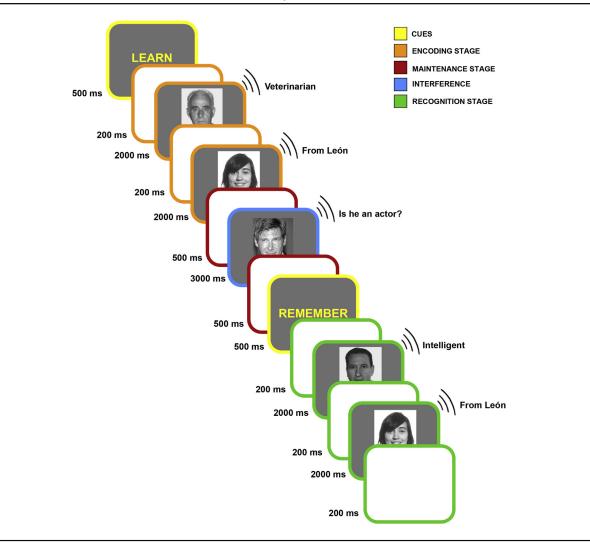
MEG Data Collection and Source Analysis

MEG signals were recorded continuously during the execution of the memory task with a 148-channel whole-head magnetometer array (Magnes 2500 WH; 4-D Neuroimaging Inc., San Diego, CA). Data were sampled at 678.17 Hz and band-pass filtered between 0.1 and 50 Hz. Electro-oculogram activity was recorded at the same sampling rate and online filter by using a Synamps amplifier (NeuroScan, El Paso, TX) with Ag/AgCl electrodes. MEG data were initially submitted to an off-line noise reduction procedure included in the 4-D Neuroimaging signal analysis package. Ocular artifacts were corrected using a BESA (MEGIS Software GmbH, Gräfelfing, Germany) artifact correction tool.[27] Data were visually inspected for movement artifacts, and trials with amplitudes above 3 pT were discarded.

Artifact-free 1,000-millisecond epochs from the encoding stage that were followed by a correct recollection period were averaged together with a 100-millisecond prestimulus baseline for each channel, subject, and experimental condition. The resulting event-related fields (ERFs) were in all cases averages of at least 90 epochs. Finally, they were digitally filtered with a 20-Hz low-pass filter.

A minimum norm estimation procedure[28,29] was applied to estimate the cortical origin of the ERFs. For the estimation of the current source distribution, a tessellated cortical mesh template surface derived from the Montreal Neurological Institute (MNI) phantom brain and implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) served as a brain model. This MNI dipole mesh (7,204 nodes) was used to calculate the forward solution using a head model based on local overlapping spheres. Thereby, local spheres were fitted to the underlying head shape points for each channel. It has been shown that a local spheres model constitutes a good approximation to a realistic head model in the case of MEG.[30] The inverse solution was calculated by applying l2 minimum norm estimation procedures,[29] with standard Tikhonov regularization[31] as implemented in the brainstorm open source toolbox (http://neuroimage.usc.edu/brainstorm/). The source strength at each node of the MNI phantom brain was estimated for each subject and experimental condition.

FIGURE 1. Example of 1 of 120 trials of the delayed match-to-sample task. Participants encoded two items and later determined whether they matched the two recognition items presented. In the meantime (during the maintenance period), the face of a celebrity (a very well-known person in Spain) and an auditory "yes/no" question about the celebrity were presented in the IC. Participants were instructed to answer the question by pressing one of two buttons. In the DC, only the face of a celebrity was presented during the maintenance period. Participants had to press any of the two buttons for possible differences between conditions due to motor activity.

Statistical Analysis

Two-sample *t*-tests between age groups were simultaneously performed for each of the mesh nodes and time points, for both IC and DC. To account for the multiple comparisons problem in a situation involving a large number ($7{,}204 \times 746$) of simultaneous tests, the *false discovery rate* control procedure of Benjamini and Hochberg[32,33] was applied using a *q*-value $= 0.1$.

RESULTS

Behavioral Results

Behavioral performance at recognition was calculated by means of two measures: 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, older) as between-subjects factor. Results from the analysis of variance revealed a significant effect of age on hit rates for both IC ($F_{[1, 26]} = 17.368$, p <0.0001; younger adults: 81.44% ± 5.11%; older adults: 67.43% ± 11.75%) and DC ($F_{[1, 23]} = 15.991$, p <0.001; younger adults: 87.62% ± 7.65%; older adults: 72.42% ± 10.92%), indicating that younger participants were more accurate than older participants at the recognition stage in both experimental conditions.

No significant age group effects were found for the reaction time neither in the IC ($F_{[1, 26]} = 1.058$, p = 0.314; younger adults: 610.20 ± 139.92 milliseconds; older adults: 665.17 ± 135.53 milliseconds) nor in the DC ($F_{[1, 23]} = 0.182$, p = 0.674; younger adults: 573.54 ± 78.17 milliseconds; older adults: 587.09 ± 76.89 milliseconds).

MEG Results

In the DC, the elderly showed a significant enhancement of neuromagnetic activity in prefrontal areas with respect to the younger group. Specifically, the elderly were characterized by increased source strengths in the left ventrolateral prefrontal cortex (Figure 2) at latencies between 140 and 150 milliseconds.

In the IC, there was a significant increase of source activity in the right ventral prefrontal cortex (right VPFC) and the right medial prefrontal cortex (Figure 3) in favor of the older group and at latencies between 155 and 165 milliseconds.

CONCLUSION

The focus of this study was on the neuromagnetic brain activity underlying memory mechanisms at the encoding stage when interfering stimuli, which did not prevent future recollection, were presented. Specifically, differences between the cortical neuromagnetic spatiotemporal activity patterns of younger and older subjects were studied in the context of a WM task with two levels of interference.

MEG results reveal age-related modulations of the cortical activity patterns during the encoding of new information in both DC and IC. This is in line with previously described changes in executive processes

FIGURE 2. Multiple comparisons corrected differences in neuromagnetic brain activity between age groups in the DC. Older participants showed increased left ventrolateral prefrontal cortex activity relative to young participants at early latencies (140−150 milliseconds).
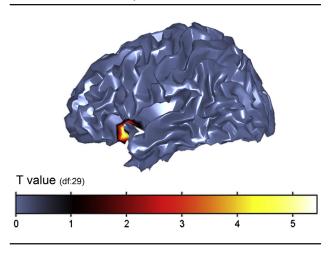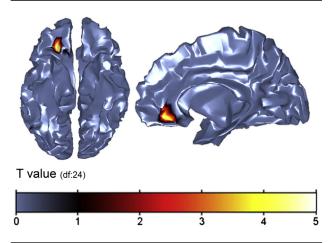

FIGURE 3. Multiple comparisons corrected differences in neuromagnetic activity between age groups in the IC. Older participants showed increased left ventrolateral prefrontal cortex and right medial prefrontal cortex activity relative to young participants at early latencies (155−165 milliseconds).

in the normal elderly.[21−25] Overall, a prefrontal activity enhancement was observed in the older group as compared with the younger one in both experimental conditions. Similar enhancement in frontal areas in older subjects has been reported before.[10,34,35]

In the DC, the older group showed a significant enhancement in left VLPFC. This area has been related to the use of semantic processing strategies[36−42] and episodic information recovery.[43−45] Furthermore, some studies have found increased activity in left VLPFC associated with the encoding of new information[46] and semantic or phonologic associations that are successfully recalled later.[47]

In the IC, older participants also showed a neuromagnetic activity increase in the ventral and medial prefrontal cortexes of the right hemisphere. It is pertinent to note that studies such as those of Rypma et al.[48,49] observed activity augmentations in right prefrontal regions with increasing task difficulty. Stronger activation of the anterior cingulate cortex (ACC) has been proposed to be related to selective attention processes, divided attention, interference resolution, and preparatory control.[50−54] Some studies have also reported ACC activations in tasks requiring inhibitory control, suggesting that this area, together with other frontal regions, plays a key role in top down attentional control.[55,56] Moreover, there exists previous MEG evidence of an early ACC activation in preparatory set shifting.[57]

In both DC and IC, enhancements of neuromagnetic activity in the frontal cortex were observed at early latencies around 150 and 160 milliseconds, respectively. This suggests an increase of top-down control, perhaps aimed to devise memory strategies against possible interferences during the maintenance period.

Taken together, these results suggest that the introduction of interfering information during the maintenance stage of a WM task produces changes in cortical activity patterns in the previous encoding process. This is consistent with the notion that older people use additional resources to prevent forgetting under interference conditions. Furthermore, these changes seemed to depend on task difficulty, given that the interruption resolution requires the recruitment of the right hemisphere. The involvement of the right cingulate has been proposed to be especially relevant in highly demanding tasks that require increased attentional control, interference resolution, and preparatory strategies.

However, one may be concerned about the possibility that others factors related to worsening of performance such as de-differentiation of neural tissues in responding to sensory inputs or failure to resolve competition among brain regions. Several points lead us to suggest a compensatory meaning as the most plausible interpretation. First, a review of the existing literature shows age-related enhancement of activity in prefrontal areas during successful memory performance as a consistent finding.[9,14−16] Second, the greater prefrontal activation in the elderly during the encoding of information that is later successfully retrieved, while the behavioral general performance during the WM task is lower among older participants than among younger participants (see Behavioral Results), lead us to suggest that this age-related enhancement of prefrontal activity reflects a compensatory mechanism in the elderly to obtain a successful retrieval. And finally, during the IC, older participants show an additional overactivated region located over the ACC, which has been related to selective attention processes, interference resolution, and preparatory control[50−54] and has also been observed strongly activated in tasks requiring inhibitory control.[55,56] Finding this area more active among older volunteers than among young volunteers during trials that are later successfully recognized in the condition that requires more executive control, specifically more inhibitory control and interference resolution, points to the compensatory theory as a more plausible interpretation than the de-differentiation explanation.

Although the most suitable way to discard the possibility that the additional activation is due to worsening of performance would be to compare the older participants' brain activity between successful and unsuccessful performance, the limited number of error trials in our experiment (and the consequential low signal-to-noise ratio of the resulting ERFs) prevented us from applying source reconstruction to the corresponding data. Although the conjunction of the three previous points seems to reasonably support the compensatory interpretation more than others, we cannot absolutely discard a possible contribution of de-differentiation process in the increased activation found in the elderly.

Although the main objective of this study were the age-related changes in brain activity that characterize the encoding of information later on successfully retrieved in the context of interference, the effect of the interference itself is an issue still open. Further studies should include an additional condition without any interference to isolate the effect of interference in relation to pure maintenance.

A final potential limitation of this study is about the *false discovery rate* control procedure used to account for the multiple comparisons problem. It is important bear in mind that using a *q*-value = 0.1 implies that 10% of dipoles declared significant after the multiple comparisons correction are expected to correspond to false-positive results.

To summarize, our results allow for the following conclusions: 1) in a WM task with two levels of interference during the maintenance period, older participants showed stronger activation of prefrontal areas than younger subjects at early latencies of the encoding stage; 2) these areas have been previously related to the processing depth of information, the encoding of new information, and successfully recalled semantic associations; 3) interference provoked enhancement of activity in brain areas related to attentional control, interference resolution, and preparatory control in the elderly as compared with the young; and 4) these changes could reflect higher top-down influences on information processing in the elderly representing compensatory mechanisms underlying the encoding of items that are successfully retrieved later.

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