

Variable effects of aging on frontal lobe contributions to memory

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Declarative memory declines with age, but there is profound variation in the severity of this decline. Healthy elderly adults with high or low memory scores and young adults viewed words under semantic or non-semantic encoding conditions while undergoing fMRI. Young adults had superior memory for the words, and elderly adults with high memory scores had better memory for the words than those with low memory scores. The elderly with high scores had left lateral and medial prefrontal activations for

semantic encoding equal to the young, and greater right prefrontal activation than the young. The elderly with low scores had reduced activations in all three regions relative to the elderly with high memory scores. Thus, successful aging was characterized by preserved left prefrontal and enhanced right prefrontal activation that may have provided compensatory encoding resources. *NeuroReport* 13:2425–2428 © 2002 Lippincott Williams & Wilkins.

Key words: Ageing; Encoding; Memory; Prefrontal cortex

INTRODUCTION

Declarative or episodic memory declines in older adults [1], but there are profound individual differences among the elderly in the severity of that decline [2]. Disproportionate and focal decline of declarative memory in some elderly has been described as age-associated memory impairment (AAMI) or mild cognitive impairment (MCI) [3,4]. This substantial variation in the severity of age-associated memory decline may reflect variability of age-associated changes in the neural systems that mediate memory in the human brain.

Functional neuroimaging methods have visualized age-associated changes in both the encoding and retrieval of declarative memories. Most imaging studies have observed reduced activation, especially in prefrontal cortex, in elderly relative to young people during the encoding of experience into long-term memory [5–7] (but see [8]). In one study [7] the magnitude of left prefrontal activation during the semantic encoding of words in the elderly correlated positively with neuropsychological measures of declarative memory. Thus, age-related reductions in prefrontal activation may reflect the average of preserved activation in older adults with better memory ability and reduced activation in older adults with worse memory ability. Consequently, the average activations of elderly people in prior imaging

studies may have underestimated the degree of preserved prefrontal function in successfully aging older individuals.

The goal of the present study was to determine whether prefrontal activations during declarative memory encoding differ substantially between older adults with better or worse memory abilities, and to compare these activations to those seen in young adults. We therefore identified non-demented, healthy older adults with relatively high or low scores on tests of declarative memory. These two elderly groups and young participants performed a memory encoding task in which words were semantically or non-semantically encoded. Semantic, relative to non-semantic, encoding enhances later memory for words [9] and yields activation in left prefrontal cortex in young adults [10–12] and in old adults [7,8]. Greater left prefrontal activation during the encoding of a word is correlated with the likelihood of subsequent memory for the word [11].

An additional question of interest related to possible age-associated changes in the lateralization of prefrontal activation. Many imaging studies have observed reduced asymmetry of prefrontal activations in older relative to younger people [13,14] and this has been seen for semantic encoding [7,8]. Enhanced contralateral prefrontal activations in the elderly may reflect compensatory processes used to ameliorate diminished efficacy of function in the dominant

frontal hemisphere [13,14]. In the present study, therefore, it was hypothesized that relatively good memory performance in older adults may involve compensatory recruitment of right prefrontal cortex during semantic encoding.

MATERIALS AND METHODS

Participants: There were 14 healthy, older adult participants (three male, 11 female; mean age 71 years, range 61–81; mean education 16.3 years, range 13–19) and eight young participants (five male/three female; mean age 24 years, range 19–33; mean education 17.3 years, range 15–24). Older adults were recruited from a group of 120 individuals who had been followed for 8 years prior to the current study [15,16]. Participants were screened for known neurological, psychiatric, and vascular risk factors or any medication that might affect vascular reactivity or cognitive performance. Older participants were divided into high and low memory groups based on their most recent memory screening (2 years prior to imaging). Performance of high and low memory groups were significantly different ($t(12)=9.25$, $p < 0.0001$) on the average proportion correct on four memory tests that served as the basis for their selection: Wechsler Memory Scale subtests Logical Memory (WMS-LMI) and Paired Associates (WMS-PAI) immediate recall [17], Benton Visual Retention Test-Revised (BVRT-R) [18], and a locally developed memory recall task (MR). There was no significant difference ($p > 0.1$) between the groups for age, years of education, mini-mental state examination (MMSE) [19], or single word reading (American modification of the National Adult Reading Test; AMNART) [20]. Participants provided informed consent and were paid for participation.

Experimental paradigm: In two scans, participants made two kinds of judgments for words. During the semantic judgment task, participants decided whether each word referred to a manufactured or naturally occurring object, pressing a response button with the right index finger if the word referred to a manufactured object. During the case judgment task (baseline), participants decided whether each word was printed in upper or in lower case letters, pressing a response button with the right index finger if the word appeared in uppercase. In each scan, the two encoding tasks alternated five times (10 blocks) every 25.92 s with 10 words per block (total time per scan = 259.2 s). Half of the words in each block were manufactured, the other half referred to naturally occurring entities. Half of the words appeared in uppercase, the remaining half in lowercase. Each word appeared for 2 s with a 593 ms interstimulus interval. The presentation of stimuli and collection of behavioral data was accomplished using a millisecond timer interfaced with a Macintosh computer running PsyScope [21]. After completing one of the encoding conditions, participants performed a recognition memory test in which half the words had been semantically encoded (old) and half were new.

Imaging parameters and analyses: Participants underwent two functional MRI (fMRI) imaging scans on a 1.5 T GE Signa scanner (General Electric Medical Systems Signa, Rev. 5.5, Waukesha, Wisconsin) using a spiral acquisition sequence (TR = 1080 ms, TE = 40 ms, flip angle = 78°,

FOV = 360 mm, and acquired inplane resolution = 2.2 mm, 12 contiguous, coronal, 7 mm slices, number of excitations = 2). Slices were acquired over the frontal lobe only, anterior to the anterior commissure and perpendicular to the plane defined by the anterior and posterior commissures.

Data were analyzed using SPM99 [23] implemented in MATLAB (Version 5.2 Mathworks, Inc., Sherborn, MA). Functional images were motion corrected and a model (a box-car reference function, corresponding to the time course of the Semantic and Case conditions convolved with an estimate of the hemodynamic response function) was fitted to the fMRI timeseries data from each participant. A volume, consisting of a weighted linear combination of parameter estimates at each voxel for the comparison of interest (semantic/case judgments) was computed for each participant (young, old high memory, old low memory). These volumes were normalized into a common stereotactic space (template provided by the Montreal Neurological Institute), scaled to an overall grand mean of 100, and entered in a random effects analysis [22], specifically, a *t*-test evaluating whether the parameter estimates for the semantic/case contrast were significantly different from 0, with the degrees of freedom reflecting the number of subjects minus one. Regions of interest (ROI) were selected by first applying an uncorrected threshold of $p < 0.001$ and then a correction for spatial extent [24] of corrected $p < 0.05$ using the theory of Gaussian fields as implemented in SPM99. Activations in those ROIs were compared in one-tailed *t*-tests between young and high memory elderly and between high- and low memory elderly.

RESULTS

Behavioral performance: Encoding accuracy was scored as the proportion of hits:false alarms and analyzed in an ANOVA with factors of groups (young, old high memory, old low memory) and tasks (semantic judgment, case judgment). Data from one of the participants in the old low memory group was lost for technical reasons. For encoding, participants were more accurate on the case (0.96) than the semantic judgment (0.84) task ($F(1,18)=79.9$, $p < 0.0001$). This probably reflects the unambiguous nature of case judgments and the more ambiguous nature of semantic judgments for which there were alternative interpretations of some words. There was not a significant difference among the groups.

Recognition accuracy was scored as the proportion of hits:false alarms and analyzed in an ANOVA (young, old high memory, old low memory). Data from one of the participants in the old low memory group was lost for technical reasons. All three groups differed ($F(2,18)=9.37$, $p < 0.01$). Specifically, a Newman-Keuls *post-hoc* comparison ($p < 0.05$) confirmed that young (mean \pm s.d. 0.77 ± 0.12) performed better than old high memory (0.59 ± 0.16) who, in turn, performed better than old low memory (0.42 ± 0.18).

Functional imaging results: Semantic judgment, relative to case judgment, yielded multiple frontal activations across all participants (Fig. 1; Table 1). Three of the largest ROIs in the inferior left, inferior right, and medial/pre-SMA frontal

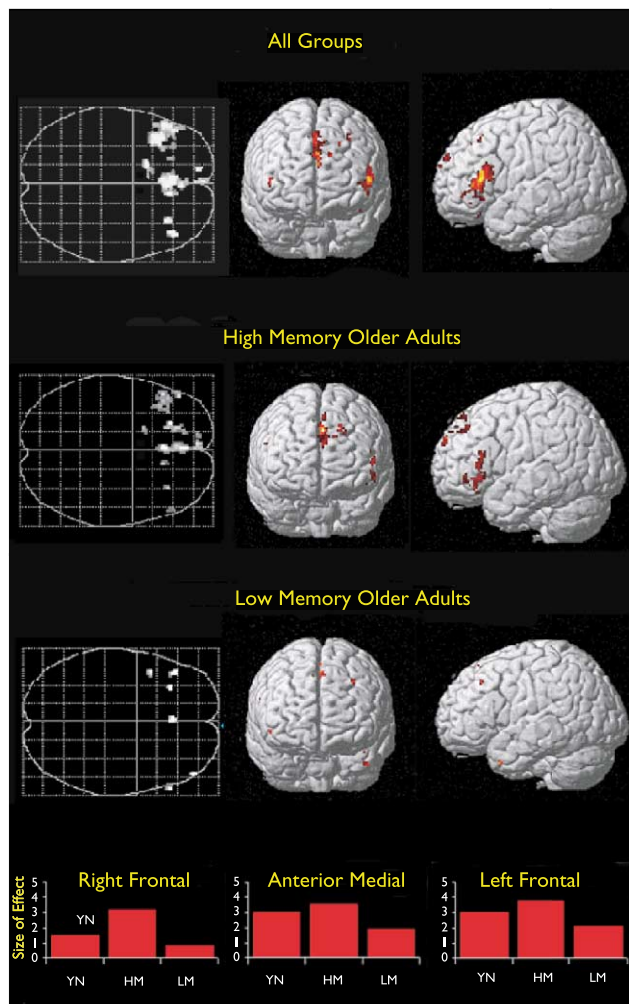


Fig. 1. Top row displays the main effect of condition (semantic versus case judgment) across all three groups (young, high memory, low memory; intensity threshold $p < 0.001$, minimum cluster size of 5). The second and third rows display activation maps generated from two, separate, random effects, ANOVAs of high memory ($n = 7$) and low memory groups ($n = 7$; intensity threshold $p < 0.001$, minimum cluster size of 5 voxels). The left column shows axial projection maps and the middle and right columns show frontal and left hemisphere activation projected on a rendered brain. The bottom row displays a histogram of the weighted parameter estimates (beta) within the left, right, and medial ROIs.

regions were selected for further analysis. The high memory older group differed significantly from the young group only in the right frontal ROI where they had greater activation than the young group ($t(12) = 1.83$, $p < 0.05$). The high memory group demonstrated higher levels of activation than the low memory group in the medial frontal ($t(12) = 2.47$, $p < 0.05$), left frontal ($t(12) = 2.05$, $p < 0.05$), and right frontal ($t(12) = 2.97$, $p < 0.05$) regions. None of the comparisons of the low memory group with the young approached significance.

DISCUSSION

Aging had variable effects on memory ability and the frontal lobe memory systems that enhance the semantic encoding of words into declarative memory. Older adults with higher memory ability showed preserved left inferior and anterior medial prefrontal activation, and enhanced right inferior prefrontal activation. Older adults with lower memory ability had reduced activations in all frontal regions, and did not show disproportionate enhancement of right prefrontal activation. There are numerous methodological challenges in interpreting fMRI differences between older and younger adults, including age-associated changes in the amplitude or variability of the BOLD vascular response and in gray matter volumes. These issues do not complicate the comparison of high- and low memory adults. Indeed, the effects of aging were so profoundly different that the low memory group had significantly less activation in all frontal ROIs despite the relatively small sample sizes.

These findings may reconcile an apparent difference between the two prior studies that examined prefrontal activation in older adults during semantic encoding. One study found reduced left prefrontal and preserved right prefrontal activation [7], whereas another study found preserved left prefrontal and enhanced right prefrontal activation [8]. The present study suggests that both of these findings occur in healthy older people, and the specific finding depends upon the memory ability of the healthy older participants in a given study.

These results favor the view that the contralateral enhancement of prefrontal activation often observed in the elderly [13,14] reflects compensatory recruitment of additional resources to ameliorate the deleterious influence of age upon dominant hemisphere neural systems. Older people with higher memory exhibited a disproportionate right prefrontal activation so great that it exceeded the activation of young adults. Older people with lower

Table 1. Regions showing more activation for semantic than case judgments.

Region	Coordinates	Coordinates			Magnitude (T)	Spatial (p)	Volume (mm^3)
		x	y	z			
Medial frontal	BA8	0	33	39	6.88	0.001	2608
	BA10	-2	63	17	5.24	0.012	192
Left frontal	BA44/45	-42	20	10	6.50	0.001	2752
	VL/VA/DMN	-16	11	-7	6.13	0.015	184
Right frontal	BA45/46	44	35	4	5.54	0.015	184
	BA47	32	9	-6	5.25	0.035	152

Regions reflect a main effect of condition (semantic vs case judgments) for all three participant groups (intensity threshold of uncorrected $p < 0.001$; extent threshold corrected $p < 0.05$). Coordinates are represented in Talairach and Tournoux stereotactic space. BA = Brodmann area.

memory did not show a disproportionate right frontal activation, and the right frontal activation was less than that of the high memory elderly. Thus, in this study, disproportionate contralateral activation was associated specifically with relatively good memory performance in the elderly.

Focal declines in memory ability have been termed MCI, and shown to be a major risk factor for conversion to AD [4,25]. The older adults in this study also participated in a larger structural imaging study that measured the volumes of entorhinal cortex and hippocampus. The low memory group in this study had reduced entorhinal volumes relative to the high memory group. Reduced entorhinal cortex appears to be the most reliable differentiator between healthy cognitive aging and MCI, and also the best predictor of conversion to AD [26]. Thus, the current study suggests an association between reduced entorhinal volume and reduced prefrontal activation that may characterize MCI and be the hallmark of a prodromal stage of AD. Longitudinal studies will be needed to verify whether age-related reductions in prefrontal activation reveal increased risk for AD.

CONCLUSION

These findings show that aging can vary greatly in its effect on memory performance and on the functional integrity of prefrontal regions that enhance the encoding of experience into long-term declarative memory. Older adults with relatively good memory ability exhibited left inferior and anterior medial prefrontal activations that were equal in magnitude to those of young adults, and a right inferior prefrontal activation significantly greater than young adults. The enhanced contralateral activation may reflect the successful compensatory recruitment of additional resources to maximize memory performance. Older adults with worse memory ability had reduced activation relative to older adults with good memory ability, and did not show enhanced contralateral activation. Thus, there are major

differences in prefrontal activation between older adults with more or less successful aging of memory ability.

REFERENCES

1. Craik FI. *Curr Dir Psychol Sci* **3**, 155–158 (1994).
2. Craik FI, Byrd M and Swanson JM. *Psychol Aging* **2**, 79–86 (1987).
3. Crook TH, Bartus RT, Ferris SH *et al.* *Dev Neuropsychol* **2**, 261–276 (1986).
4. Petersen RC, Stevens JC, Ganguli M *et al.* *Neurology* **56**, 1133–1142 (2001).
5. Grady CL, McIntosh AR, Horwitz B *et al.* *Science* **269**, 218–221 (1995).
6. Cabeza R, Grady CL, Nyberg L *et al.* *J Neurosci* **17**, 391–400 (1997).
7. Stebbins GT, Carrillo MC, Dorfman J *et al.* *Psychol Aging* **17**, 44–55 (2002).
8. Logan JM, Sanders AL, Snyder AZ *et al.* *Neuron* **33**, 827–840 (2002).
9. Craik FIM and Lockhart RS. *J Verbal Learn Verbal Behav* **11**, 671–684 (1972).
10. Gabrieli JDE, Desmond JE, Domb JB *et al.* *Psychol Sci* **7**, 278–283 (1996).
11. Wagner AD, Schacter DL, Rotte M *et al.* *Science* **281**, 1188–1191 (1998).
12. Kapur S, Craik FI, Tulving E *et al.* *Proc Natl Acad Sci USA* **91**, 2008–2011 (1994).
13. Cabeza R. *Psychol Aging* **17**, 85–100 (2002).
14. Reuter-Lorenz PA, Jonides J, Smith EE *et al.* *J Cogn Neurosci* **12**, 174–187 (2000).
15. McKittrick LA, Friedman LF, Brooks JO *et al.* *Int Psychogeriatr* **11**, 289–300 (1999).
16. O'Hara R, Yesavage JA, Kraemer HC *et al.* *J Am Geriatr Soc* **46**, 1493–1498 (1998).
17. Wechsler D. *Manual for the Wechsler Memory Scale*. New York: Psychological Corporation; 1956.
18. Benton AL. *Revised Visual Retention Test*. New York: The Psychological Corporation; 1974.
19. Folstein MF, Folstein SE and McHugh PR. *J Psychiatr Res* **12**, 189–198 (1975).
20. Nelson HE and O'Connell A. *Cortex* **14**, 234–244 (1978).
21. Cohen J, MacWhinney B, Flatt M *et al.* *Behav Res Methods Instr Comput* **25**, 257–271 (1993).
22. Holmes AP and Friston KJ. *Neuroimage* **7**, S754 (1998).
23. Friston KJ, Holmes AP, Worsley KJ *et al.* *Hum Brain Mapp* **2**, 189–210 (1995).
24. Friston KJ, Worsley KJ, Frackowiak RSJ *et al.* *Human Brain Mapp* **1**, 214–220 (1994).
25. deToledo-Morrell L, Goncharova I, Dickerson B *et al.* *Ann NY Acad Sci* **911**, 240–253 (2000).
26. Killiany RJ, Hyman BT, Gomez-Isla T *et al.* *Neurology* **58**, 1188–1196 (2002).

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