Age-Related Differences in Neural Activity during Item and Temporal-Order Memory Retrieval: A Positron Emission Tomography Study

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Abstract

■ Positron emission tomography (PET) was used to investigate the hypothesis that older adults' difficulties with temporal-order memory are related to deficits in frontal function. Young (mean 24.7 years) and old (mean 68.6 years) participants studied a list of words, and were then scanned while retrieving information about *what* words were in the list (item retrieval) or *when* they occurred within the list (temporal-order retrieval). There were three main results. First, whereas the younger adults engaged right prefrontal regions more during temporal-order retrieval than during item retrieval, the older adults did not. This result is consistent with the hypothesis that context memory deficits in older adults are due to frontal dysfunction. Second, ventromedial temporal activity during item memory was relatively unaffected by aging. This finding concurs with evidence that item memory is relatively preserved in old adults and with the notion that medial temporal regions are involved in automatic retrieval operations. Finally, replicating the result of a previous study (Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., Houle, S., & Craik, F. I. M., 1997), the old adults showed weaker activations than the young adults in the right prefrontal cortex but stronger activations in the left prefrontal cortex. The age-related increase in left prefrontal activity may be interpreted as compensatory. Taken together, the results suggest that age-related changes in brain activity are rather process- and region-specific, and that they involve increases as well as decreases in neural activity. ■

INTRODUCTION

The present study was motivated by three well-supported findings. First, structural and functional changes in the frontal lobes contribute to older adults' memory problems (for a review, see West, 1996). Volumetric analyses of structural MRI data indicate that age-related atrophy is most prominent in the prefrontal cortex (Raz et al., 1997). Also, in PET studies, frontal activations are weaker for older adults during both encoding (Cabeza et al., 1997a; Grady et al., 1995) and retrieval (Cabeza et al., 1997a; Schacter, Savage, Alpert, Rauch, & Albert, 1996). Second, context memory depends more on frontal function than does content memory (for a review, see Schacter, 1987). Content memory—also called item memory—refers to *what* events occurred in the past, whereas context memory refers to *when* (temporal-order memory), *where* (spatial memory), or *how* (source memory) they happened. The differential involvement of frontal regions in context memory is particularly clear in the case of temporal-order memory. For example, frontal lesions in human (Milner, 1971; Shimamura, Janowsky, & Squire, 1990) and nonhuman (Petrides, 1991) primates produce greater impairments of temporal-order memory than of item memory. Extending those findings to the intact brain, we recently

Table 1. Demographic and Neuropsychological Data

	Young Ss	*Old Ss*
Age	24.7	68.6*
Education (years)	18.2	17.2
Word fluency (FAS)	43.9	43.1
Word fluency (food)	25.1	22.0
Vocabulary (Mill Hill)	22.3	27.8*
Word Recall (CVLT 1–5)	64.6	55.5*
SOP Errors (1–3)	2.5	5.6*
WCST % errors	8.3	17.8*
WCST categories	5.9	3.4*

Notes: SOP=Self-ordered pointing test; WCST=Wisconsin card sorting test

*$p<.05$.

showed using PET that prefrontal regions were more activated during temporal-order retrieval than during item retrieval (Cabeza et al., 1997c). Third, age-related impairments generally are greater in context memory than in content memory. A meta-analysis of 46 studies showed reliably greater age-related decrements in context memory than in content memory, particularly when spatio-temporal context is involved (Spencer & Raz, 1995).

Taken together, these findings suggest that context memory is particularly sensitive to aging because it depends on a brain region that is especially affected by aging: the frontal lobes. However, the evidence linking context memory deficits in old adults to frontal dysfunction is indirect. For example, Parkin, Walter, & Hunkin (1995) found that older adults' temporal-order memory performance, but not their item memory performance, was positively correlated with performance on a test assumed to reflect frontal function (semantic fluency). In order to establish a direct link between older adults' context memory deficits and altered frontal functions, we used PET to compare brain activity in young and old adults during item and temporal-order memory retrieval.

Healthy young and old participants (see Table 1) studied a list of words and were then scanned in two kinds of tests while seeing pairs of words. In the item memory test, one word of each pair was previously studied and the other was not, and subjects' task was to identify the studied word by clicking the left or the right mouse button. In the temporal-order memory test, both words were studied, and subjects' task was to indicate, by clicking a mouse button, which of the two words had appeared more recently in the study list. Chance probability of a correct response in both of these two-alternative forced-choice tasks is .50. Encoding conditions were manipulated so that each test would have two significantly different levels of difficulty, easy and hard. The rationale for crossing the task-type manipulation with a task-difficulty manipulation was to differentiate between brain activity associated with qualitative differences between the tasks and brain activity associated with quantitative differences in performance levels.

We had three expectations. First, on the basis of the aforementioned findings, we predicted less frontal activity during temporal-order retrieval in old adults than in young adults. Second, we predicted small age-related differences in ventromedial temporal activity during item retrieval. This expectation was based on the fact that item-memory performance is only modestly affected by aging (Spencer & Raz, 1995), and that ventromedial regions, which are engaged by young adults during item memory (Cabeza et al., 1997c), are relatively resistant to the effects of aging on brain structure (Raz et al., 1997) and function (Schacter et al., 1996). Finally, we expected to replicate the asymmetric effect of aging on frontal activity found in our previous study (Cabeza et al., 1997a), where old adults showed weaker activations than young adults in the right prefrontal cortex, but stronger activations in the left prefrontal cortex.

RESULTS

Behavioral Data

The behavioral results (see Table 2) reveal that memory performance was higher in young than in old adults, in the item than in the temporal-order retrieval test, and in the easy than in the hard condition. Confirming these impressions, a 2 (age: young vs. old) ×2 (task: item vs. temporal-order) ×2 (difficulty: easy vs. hard) ANOVA yielded significant main effects of age [$F(1,20)=5.3$, $p<.04$], task [$F(1,20)=48.3$, $p<.0001$], and difficulty [$F(1,20)=25.5$, $p<.0001$]. This analysis also showed a significant interaction between task and difficulty [$F(1,20)=16.05$, $p<.0005$], due to the relatively greater effect of difficulty on the item-memory task than on the temporal-order memory task. The interaction between age and task [$F<1$] and the 3-way interaction between age, task, and difficulty did not reach significance [$F(1,20)=3.7$, $p<.07$].

Even though the task×age interaction was not reliable, the age effect was clear in the temporal-order condition, but not in the item condition. Separate two-

Table 2. Behavioral Data: Proportion Correct (SD)

	Young Ss	*Old Ss*
Item-easy	.90 (.06)	.82 (.12)
Item-hard	.73 (.13)	.68 (.09)
Order-easy	.72 (.11)	.57 (.14)
Order-hard	.61 (.10)	.58 (.13)

Note: .50=chance

tailed t-tests indicated that the effect of aging was marginally significant in the temporal-order condition [$t(20)=2.0$, $p=.055$] but nonsignificant in the item condition [$t(20)=1.7$, $p=.10$]. Moreover, when considering only the conditions in which item and temporal-order memory performance were matched in young adults (item-hard and order-easy), the age effect was definitely significant in the temporal-order condition [$t(20)=2.8$, $p=.01$], and nonsignificant in the item condition [$t(20)=1.1$, $p=.28$]. Thus, old adults were impaired in temporal-order retrieval, but not in item retrieval. However, given the lack of a reliable task×age interaction, it is not possible to claim that age effect was significantly larger in the temporal-order condition than in the item condition.

PET Data

Before turning to the PET results, we should mention that group differences in brain activity in a target task can be determined only in relation to brain activity in a reference task, which is also affected by group differences. Thus, an age-related decrease in the difference between a target task and a reference task may reflect an age-related decrease in activation in the target task or an age-related increase in the reference task. This problem is not solved by the inclusion of low-level sensory–motor baselines, because these conditions are also affected by group differences (for example, Grady et al., 1994). Therefore, when we talk about age-related increases and decreases in activation, we always mean increases and decreases in rCBF differences between two tasks.

Masked contrasts identified regions associated with item retrieval or with temporal-order retrieval in both the young and the old adults (see Table 3 and Figure 1a–f). Regions engaged by both groups during item retrieval included bilateral ventromedial temporal areas (Figure 1a–c) and the caudate nucleus (Figure 1d). Areas associated with temporal-order retrieval in both groups included bilateral posterior/inferior parietal regions (Figure 1e–f) and the left prefrontal cortex (Figure 1f).

In the factorial design, the main effect of task difficulty and its interactions with task type and age group did not yield significant activations; hence, their results are not reported. In contrast, several regions showed significant interactions between age group and task type (see Table 4 and Figure 1g–l). The first age X task interaction contrast detected the set of regions that the young activated more during item retrieval than during temporal retrieval or that the old activated more during temporal-order retrieval than during item retrieval. Only one activation, located in left Sylvian regions, was significant for this contrast (Figure 1g). Post hoc paired t-tests comparing peak activity in this region during item retrieval and temporal-order retrieval (see two rightmost columns of Table 4) revealed that the young adults activated the left Sylvian region more during the item retrieval task than during the temporal-order retrieval task, whereas the old adults activated this region to a similar degree in the two retrieval tasks. The second age X task interaction contrast detected regions that the young activated more during temporal-order retrieval than during item retrieval and/or that the old activated more during item retrieval than during temporal-order retrieval. Post hoc paired t-tests comparing activity during item retrieval with activity during temporal-order retrieval were conducted within age group at each site of peak activity. These tests revealed two kinds of age-related differences in brain activity that contributed to the interaction: (1) Regions more activated during temporal-order retrieval than during item retrieval in young adults but not in old adults, including the right pre-

Table 3. Item and Temporal-Order Memory: Common Regions in Young and Old Adults

Region (Slice/s Showing Activation in Figure 1)		*BA*	*Young x*	*Young y*	*Young z*	*Young z-score*	*Old x*	*Old y*	*Old z*	*Old z-score*	*# of Voxels of Overlap*
Item>Temporal-Order											
Bilateral ventromedial–temporal (a, b, c)	L	28	– 12	– 2	– 24	3.6	– 10	– 4	– 20	2.6	573[a]
	L	38	– 38	10	– 20	4.1	– 38	6	– 24	4.1	573[a]
	R	38	38	10	– 16	3.3	38	8	– 20	3.4	132
Caudate nucleus (d)			4	18	4	3.1	0	18	0	3.3	50
Temporal-Order>Item											
Bilateral parietal–occipital (e, f)	R	39	36	– 68	24	5.3	36	– 58	24	3.7	150
	L	39	– 30	– 74	24	3.4	– 26	– 72	24	2.9	121
Left prefrontal (f)	L	9	– 36	26	32	3.5	– 38	24	36	3.0	46

[a]Same cluster.

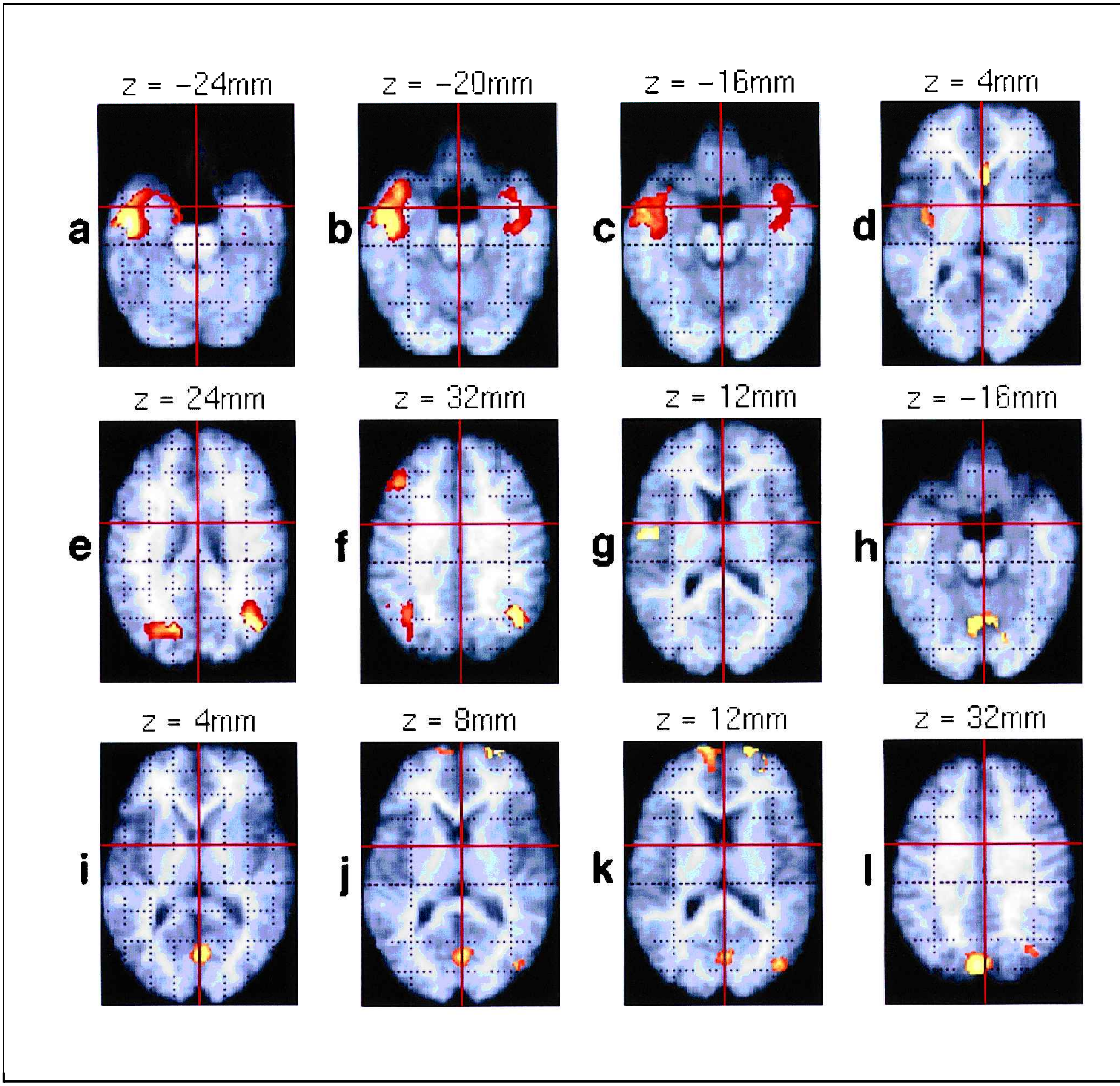

Figure 1. (a–f) Regions significantly activated in both young and older group (See Table 3). **(g–l)** Regions showing significant task (item vs. temporal-order retrieval) ×age (young vs. old) interactions (See Table 4).

frontal cortex (Figure 1j–k) and medial parieto-occipital areas (Figure 1i–l). (2) Regions more activated during item retrieval than during temporal-order retrieval in older adults but not in young adults, such as the left prefrontal cortex (Figure 1j–k) and the cerebellar vermis (Figure 1h).

DISCUSSION

The results confirmed our three expectations. First, whereas the young adults engaged right prefrontal regions more during temporal-order retrieval than during item retrieval, the old adults did not. Second, ventromedial temporal activity during item memory was relatively unaffected by aging. Finally, the effect of aging on frontal activity was asymmetric: Unlike their younger counterparts, the old adults did not differentially activate right prefrontal cortex during the temporal order task, but they did show stronger activation of left prefrontal cortex during item retrieval than during temporal-order retrieval. These three findings are discussed in separate sections below, followed by a discussion of additional results.

Before discussing the results, it is appropriate to consider a couple of issues regarding the interpretation of age-related differences in functional activation. First,

Table 4. Item and Temporal-Order Memory: Different Regions in Young and Old Adults

Region (Slice/s Showing Activation in Figure 1)	Age×Task Interactions BA	x	y	z	z-score	# of Voxels	t-score of Pairwise Contrast* Young	Old
Item>Temporal-Order in the Young but not in the Old								
Left Sylvian (g)	42	– 46	– 10	12	3.7	49	3.73	n.s.
Temporal-Order>Item in the Young but not in the Old								
Right prefrontal (j, k)	10	24	62	8	4.7	37	4.71	n.s.
Medial parieto-occipital (i, j, k, l)	19	– 4	– 78	32	4.8	106	7.42	n.s.
	18	2	– 70	0	4.1	230[a]	5.16	n.s.
Right posterior parietal (j, k, l)	39/19	34	– 78	12	3.6	27	4.38	n.s.
Item>Temporal-Order in the Old but not in the Young								
Left prefrontal (j, k)	10	– 8	64	12	3.8	38	n.s.	2.89
Cerebellum: vermis (h)		– 4	– 68	– 16	3.6	230[a]	n.s.	3.98

n.s.=nonsignificant

*t-scores are significant at $p<.05$.

[a]Same cluster.

age-related decreases in activation, generally, are assumed to reflect cognitive deficits (Cabeza et al., 1997a; Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997d; Grady et al., 1994; Grady et al., 1995; Madden et al., 1996; Schacter et al., 1996), and age-related increases, functional compensation (Cabeza et al., 1997a; Grady et al., 1994). We make these assumptions here, but know they are not always correct; for example, less activation may reflect more efficient processing (Karni, Meyer, Jezzard, Adams, et al., 1995), and more activation may reflect less efficient processing (Cabeza et al., 1997a). Second, although we interpret each age-related difference separately, we do not believe that these differences are exclusively local in nature (for example, cell loss in a certain brain region). On the contrary, we have recently demonstrated that age-related changes in neural activation are partly due to age-related changes in effective connectivity in the neural network underlying the task (Cabeza et al., 1997d).

Age-Related Decrease in Frontal Activity During Temporal-Order Memory

In young adults, the right prefrontal cortex was more activated during temporal-order retrieval than during item retrieval. This finding is consistent with evidence that frontal lesions in humans and nonhuman primates produce larger deficits on temporal-order memory tasks than on item memory tasks (for example, Butters, Kaszniak, Glisky, Eslinger, & Schacter, 1994; Kesner, Hopkins, & Fineman, 1994; McAndrews & Milner, 1991; Milner, 1971; Milner, Corsi, & Leonard, 1991; Petrides, 1991; Schacter, 1987; Shimamura et al., 1990; Squire, 1982). Similarly, source memory tends to be more sensitive to frontal lesions than does item memory (for example, Janowsky, Shimamura, & Squire, 1989). Evidence such as this has led investigators to postulate that context memory is particularly dependent on frontal-lobe functions (for a review, Schacter, 1987). Accordingly, context memory deficits in old adults have been attributed to deficits in frontal function (see Spencer & Raz, 1995), but the only supporting data have been correlational (for example, Craik, Morris, Morris, & Loewen, 1990; Parkin et al., 1995). The present results provide the first direct evidence that context memory deficits in old adults are related to compromised frontal functions. In contrast to the young adults, the old adults did not show an increase in right frontal activation during temporal-order retrieval relative to item retrieval, suggesting impaired temporal-order retrieval mechanisms in old age.

The interpretation of this finding depends on how the role of the prefrontal cortex in context memory is conceptualized. One possibility is that context memory is particularly dependent on a general cognitive function mediated by prefrontal regions, such as attention, working memory, or inhibition (Mangels, 1997). In this sense, the age-related reduction of frontal activity during temporal-order retrieval would be consistent with evidence that attention, working memory, and inhibition are disrupted by aging (for reviews see, Hartley, 1992; Salthouse, 1991; Zacks & Hasher, 1997). Another alternative is that the frontal lobes play a specific role in context memory. There is evidence for functional specificity in some frontal regions (e.g., processing spatial information, Wilson, O'Scalaidhe, & Goldman-Rakic, 1993) and specialized regions could also exist for temporal-order memory. According to this view, the age-related reduction of frontal activity during temporal-order retrieval would be independent of general differences in cognitive abilities. The present results do not clearly favor one interpretation over the other; however, the null main effect and interactions involving task difficulty support the conclusion that age-related impairments in temporal-order retrieval are related to specific characteristics of context memory retrieval rather than to differences in working memory load.

Small Effects of Aging on Ventromedial Temporal Activity During Item Memory

Ventromedial temporal regions were similarly engaged by the two age groups during item retrieval, a result which is consistent with evidence for structural and functional preservation of these regions with age. First, volumetric analyses of MRI data have shown that age-related atrophy in medial temporal regions is relatively mild or nonsignificant; the parahippocampal gyrus, for example, does not show significant shrinkage with age (Raz et al., 1997). Second, PET studies of episodic memory retrieval have shown that medial temporal regions play a critical role in item retrieval (for example, Nyberg, McIntosh, Houle, Nilson, & Tulving, 1996b), and that activation of these regions can be preserved by aging (Schacter et al., 1996) or even increase with age (Backman et al., 1997). The pattern of compromised right frontal activity paired with a relatively preserved ventromedial–temporal activity is consistent with a theory concerning the role of these regions in episodic memory proposed by Moscovitch and Umilta (1990,1991). According to this view, medial-temporal regions are involved in automatic associative retrieval processes, such as item recognition, whereas frontal regions are involved in controlled strategic retrieval processes, such as temporal-order retrieval. Automatic processes are assumed to be more resistant to aging than are controlled processes (Hasher & Zacks, 1979). The present results concur with this view.

Asymmetric Effect of Aging on Frontal Activity

The differential involvement of left prefrontal cortex during item retrieval among the older adults replicates a finding of our previous PET study of memory and aging (Cabeza et al., 1997a). In that study, we found that during recall, the right prefrontal cortex was more activated in the young than in the old, whereas the left prefrontal cortex was more activated in the old than in the young. Therefore, in two different PET studies—employing different subjects, methods, and materials—the effect of aging on brain activity during retrieval yielded a decrease on right frontal activity paired with an increase in left prefrontal activity. We previously suggested that this pattern of activity may reflect compensation on the part of the old adults for deficits in episodic memory retrieval (mediated by right prefrontal cortex—see Nyberg, Cabeza, & Tulving, 1996a; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) through the superior use of semantic processing (mediated by left prefrontal cortex—see Cabeza & Nyberg, 2000).

When we say that an age-related increase in neural activity is compensatory, we assume that enhanced activity in the region in case was beneficial for old adults' cognitive performance, either through an improvement of the same cognitive operations employed by young adults or through the recruitment of different operations. However, determining whether an increase in activity was beneficial for performance is not a simple issue. For example, one could argue that old adults showed more activity than young adults because the task was more demanding for them than for young adults. This account is implausible in the case of the age-related increase in left prefrontal activation. This activation occurred in a condition in which memory performance in young and old adults was not reliably different. Also, if the left prefrontal activation reflects effort, then it should have been affected by the difficulty manipulation (hard vs. easy), but it was not. In contrast, the compensatory interpretation is consistent with evidence that item memory tends to be relatively preserved in old age and with recent views concerning the role of the left prefrontal cortex in episodic memory retrieval. Nolde, Johnson, & Raye (1998) recently proposed that left prefrontal activity during episodic memory retrieval increases as function of task complexity. Due to the decline in cognitive resources (for example, Craik, 1986) and processing speed (for example, Salthouse, 1996) associated with aging, the same task is likely to appear more complex for older adults than for younger adults. Accordingly, the age-related increase in left prefrontal activity may reflect a compensatory change for dealing with increased task complexity. At any rate, the compensatory hypothesis is still speculative and further research is warranted.

Additional Results

Other findings included an age-related rCBF decrease in the medial parieto-occipital cortex and an age-related rCBF increase in the cerebellar vermis. In functional neuroimaging studies, both regions are typically activated during episodic memory retrieval (for a review, see Cabeza & Nyberg, 2000). Age-related decreases in medial parieto-occipital regions included the region of the precuneus, whose role in episodic memory retrieval has been related to the use of imagery (Fletcher et al., 1995a,b). Given that imagery operations tend to decline with age (for example, Craik & Dirkx, 1992), it is possible that the age-related reduction in precuneus activation found in this study is related to impoverished imagery processes in older adults.

In contrast, the age-related increase in cerebellar activation—like the one in the left prefrontal cortex—could reflect a compensatory mechanism. This idea is consistent with evidence that the cerebellum is involved in episodic memory retrieval (for a review, see Cabeza et al., 1997b), and that its structure (Luft, Skalej, Welte, Voigt, & Klockgether, 1997) and metabolism (Loessner et al., 1995) are relatively preserved in old adults. Moreover, there is evidence that while frontal regions show hypometabolism in old adults, metabolic activity in the cerebellum may even increase with aging (Moeller et al., 1996). Volumetric analyses of MRI data have revealed age-related atrophy in the cerebellar hemispheres, but not in the anterior vermis (Raz, Dupuis, Briggs, McGavran, & Acker, 1998). Consistent with this pattern, a previous PET study showed an age-related decrease in activation in the left cerebellar hemisphere (Backman et al., 1997), whereas the present study showed an age-related increase in the vermis.

Conclusions

The present study provided three main findings. First, right frontal activity during temporal-order retrieval—as compared to that during the item retrieval—was weaker in old adults than in young adults. This is probably the first direct evidence that context memory deficits in old adults are related to altered frontal functions. Second, ventromedial temporal activity during item memory was not significantly affected by aging. This result is consistent with evidence that item memory is relatively spared by aging and with the idea that medial-temporal regions are involved in automatic retrieval processes. Finally, replicating a pattern found by Cabeza et al. (1997a), frontal activity showed an age-related decrease in right prefrontal activity coupled with an age-related increase in the left prefrontal activity. This last change could serve a compensatory function, but the idea is still speculative. In sum, the present results suggest that aging is associated with reduced right frontal activity during context memory, intact medial-temporal activity during item memory, and a more bilateral pattern of frontal activity during episodic memory retrieval.

METHODS

Participants

The participants were 12 young adults (six male, six female; age range 20–28) and 12 old adults (six male, six female; age range 60–78). One elderly male participant fell sleep during two scans and one elderly female participant did not follow the instructions of the tests. Thus, their results were excluded from all analyses. All participants were right handed and had no history of neurological or psychiatric illness. None of the participants was taking medication or had a condition that could affect cerebral blood flow (for example, high blood pressure). The young participants were mainly undergraduate and graduate students of the University of Toronto, and old participants were high-functioning community-dwelling individuals. As Table 1 indicates, the two groups were matched in education and word fluency. The old participants performed significantly better than the young participants on the vocabulary test, but performed significantly worse in word recall, self-ordered pointing, and the Wisconsin Card Sorting Test. The study was approved by the joint Baycrest Centre/University of Toronto Research Ethics and Scientific Review Committee.

Materials

From a database (Quinlan, 1992), 560 concrete nouns with a length between four and eight letters (mean: 5.5) and a frequency between 4 and 100 occurrences per million (mean: 25.8) were selected to be used as critical stimuli. The words were randomly divided into eight lists of 60 words and four lists of 20 words. The eight lists were assigned to the eight scans, and the four lists were employed as distractors in the item-retrieval tests. Other words were used as buffer items in the study lists and as practice lists. The words were presented in large black letters on a white background on a computer screen suspended 60–75 cm in front of the participants.

Procedure

The PET scanning session consisted of two blocks of four scans each, one block for the item-retrieval condition and one block for temporal-order retrieval condition. The two blocks were separated by 20 min, and the scans within each block by 11 min. The order of the two blocks was counterbalanced across participants. Before each scan, participants studied a list of words, and during the scan, they tried to retrieve them. The list length was 65 words in the item condition and 45 words in the temporal-order condition. Participants were given a short practice at the beginning of the item and temporal-order blocks to familiarize them with the study-test procedure. Two words were presented in each trial of the tests, and participants had to select as quickly and accurately as possible one of the words, by pressing either the left or the right buttons of the mouse. For the item-retrieval test (recognition), one word of each pair was from the study list and one word was new, and participants had to choose the studied word. For the temporal-order retrieval test (recency discrimination), both words of each pair were from the study list (for example, word 5 and word 15), and participants had to choose the one that appeared later in the study list (for example, word 15). In both of these two-alternative forced-choice tasks, the probability of making a correct response by chance is .50. The test lists consisted of 20 word pairs, which were presented for 4 sec each with 1-sec interval. The list started simultaneously with the injection of the tracer (about 20–25 sec before the scan window) and continued for 15–20 sec after the end of the 60-sec scan window.

In both the item and temporal-order retrieval conditions, easy and hard levels of performance were produced by manipulating presentation rate and study-test delay. The presentation rate in the item-easy, item-hard, order-easy, and order-hard conditions was respectively 2, 0.25, 5, and 2 sec per word. The inter-stimulus interval was always 0.5 sec. The study-test interval in the item-easy, item-hard, order-easy, and order-high conditions was respectively 3, 7, 2, and 3 min. These manipulations were chosen on the basis of the results of several pilot studies.

In the item condition, 20 words from the center of the list were tested, paired with distractors. In the temporal-order retrieval condition, 40 words from the study list (word 3 to word 42) were used to create 20 test pairs, by combining words separated by nine items (for example, words 3 and 13). In both the item-retrieval and temporal-order retrieval scan blocks, participants received two successive scans of the easy condition and two successive scans of the hard condition, with the order of easy and hard conditions counterbalanced across participants. List 1 was always used in Scan 1, List 2 in Scan 2, and so on. Because the order of the four conditions was counterbalanced, the assignment of the lists to the four conditions was also counterbalanced.

PET Methods

PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using a bolus injection of 35.5 mCi of $^{15}O–H_2O$. The preparation of the PET data for analysis involved three steps. First, using the software AIR (Woods, Cherry, & Mazziotta, 1992), the different images from each subject were realigned to the first image. Second, using SPM96 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA, USA), the realigned images from each subject were transformed into a standard space (Talairach & Tournoux, 1988) and smoothed using a 15-mm isotropic Gaussian kernel. Third, also using SPM96, the effects of the conditions on the regional cerebral blood flow at each voxel were estimated using a general linear model, wherein the changes in global counts are considered as a covariate (Friston et al., 1995). The effects of each comparison were estimated using linear contrasts, which yield a *t*-statistic (expressed as a *Z*-score) for a given comparison at each voxel.

We had two goals in mind when analyzing the PET data. The first goal was to identify common regions of significant activation in younger and older adults associated with item retrieval or with temporal-order retrieval. The main effect (for example, item retrieval minus temporal-order retrieval) can be misleading in this regard, as it may result from a large effect in one group but a non-significant effect in the other group. Masked contrasts (SPM96) identify regions in which the simple effect is significant in both groups. Masking one contrast (for example, item-minus-temporal in young adults) with another (for example, item-minus-temporal in old adults) yields only those voxels that showed a significant difference in *both* contrasts. Because masked contrasts involve a combined probability, a significance threshold of $Z>2.33$ ($p<.01$) was used for each group (combined probability $=.01\times.01=.0001$). Our second goal was to identify brain regions associated with item retrieval or temporal-order retrieval that demonstrated an age effect. Towards this goal, we employed a 2×2×2 factorial design with age group (young vs. old), task type (item vs. temporal-order retrieval), and task difficulty (easy vs. hard) as the factors. The significance threshold for these analyses was set to the standard $Z>3.09$ ($p<.001$ uncorrected).

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