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Neurobiology of Aging 28 (2007) 1568–1576

NEUROBIOLOGY OF AGING

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# Neural correlates of age-related verbal episodic memory decline: A PET study with combined subtraction/correlation analysis

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Received 10 August 2005; received in revised form 19 June 2006; accepted 4 July 2006
Available online 14 August 2006

**Abstract**

Using PET, we have determined the neural substrates of age-related verbal episodic memory decline. Twelve young and twelve older healthy volunteers (mean age; 22 and 59 years, respectively) were scanned while performing encoding and retrieval tasks. Retrieval performance was lower in old than in young subjects. The PET data were analyzed using a combined subtraction/correlation approach. Classic subtraction disclosed prefrontal rCBF increases common to both groups, distributed bilaterally during encoding and exclusively right-sided during retrieval, without between-group differences. The correlation analysis between PET activity during encoding and subsequent retrieval performance revealed significant correlations for the left hippocampal region in both groups, but for the right inferior frontal gyrus in the older subjects only. Thus, lower performance in older subjects during an episodic retrieval task may reflect a combination of (i) subtle encoding dysfunction, evidenced by more widespread activity-performance correlations and (ii) less efficient retrieval, as evidenced by unaltered activation pattern (as revealed by the classic subtraction method) despite reduced performance. These exploratory findings suggest the aged brain may be unable to compensate for reduced efficiency of right prefrontal cortex by additional left frontal activation.
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*Keywords:* Aging; Episodic memory; Intentional encoding; Stem-cued recall; Functional neuroimaging; Positron emission tomography

## 1. Introduction

It is now well established that normal aging is associated with a progressive decline of episodic memory function, especially with cued and free recall tasks [2,21,28]. Several PET and fMRI studies have been carried out in the last 10 years to investigate the neural substrates of this age-related change [3,6,23,34,36,38]. While studies in young adults consistently highlight the combined involvement of frontal and medial temporal regions in encoding and retrieval processes [7,15,17,40], the comparison to older subjects has yielded inconsistent findings. This may be due to methodological problems in the designs. One issue concerns the control of the level of processing during intentional encoding of verbal material, especially regarding semantic processing. For instance, Grady et al. [20] used three different conditions: shallow incidental (case of letters), deep incidental (living/non-living decision) and intentional encoding. However, the comparison deep incidental/intentional encoding will highlight differences associated with both "level of processing" and "intentionality". One possible way to control for this potential confound would be to divide up the intentional encoding condition in two sub-conditions, such as shallow intentional and deep intentional encoding. A similar problem concerns Madden et al.' study [30] in which two conditions were used: an intentional encoding task with deep processing (living/non-living decision) and a reading task (baseline) with shallow processing (case of letters). However, when planning a comparison between intentional and incidental encoding, ideally the same level of processing (either deep or shallow)

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doi:10.1016/j.neurobiolaging.2006.07.004

should be used in both tasks. Another potential confound in the behavioral paradigm concerns the order of presentation of the tasks. Thus, it is recommended that the intentional encoding condition is presented after rather than before the incidental (reading) condition so that the stimuli presented during the latter are not intentionally encoded. A third problem is with respect to the study of retrieval. Studies have overwhelmingly used recognition memory rather than recall because the latter is prone to induce speech-related motion artefacts [30]. However, age-related differences are larger for recall compared to recognition [12], so it is crucial to have a recall condition in the paradigm. Two studies have assessed the neural correlates of age-related changes in recall processes by comparing stem-cued recall to stem completion. In the first study [39], differences in frontal activation between young and old subjects were observed. However, the authors descriptively compared the activation patterns obtained in the two groups of subjects but did not assess between-group differences. In the second study [1], a direct between-group comparison was performed, which showed a trend for a difference, i.e., both groups activated the right frontal region but the old subjects activated the left frontal region more than the young. Of note, however, in their stem-cued recall task, only half of the cues referred to the words previously learnt, the other half involving simple stem completion (as with the baseline task); as semantic processing was not appropriately controlled, interpretation of the age-related difference observed is not clear.

In a previous PET study on healthy young subjects [4], we used the novel approach suggested by Tulving et al. [44] which combines the classic subtraction (i.e., categorical comparison) and the novel correlation (i.e., parametric analysis) methods to map the "What" and "How" sites, respectively. This approach allowed us to better comprehend the complementary roles of the frontal and medial temporal regions in verbal episodic function. Thus, while the classic subtraction analysis highlighted the frontal regions during both intentional encoding and stem-cued recall, the correlation analysis revealed that activity in the left medial temporal region was predictive of subsequent retrieval success.

Taking into consideration both the difficulties in drawing a coherent view from the studies performed so far regarding the changes in neural activity which may underlie the age-related episodic memory decline, and the relevant results from our previous study with young subjects using combined subtraction and correlation, we have studied a group of 12 optimally healthy older volunteers of mean age 59 years with the same paradigm, and applied this approach according to a direct between-group comparison.

Age-related cerebral reorganization can express in the classical way, i.e., as significantly more widespread and bilateral activations in old as compared to young subjects in the face of maintained performance [8]. In the case of reduced performance relative to the young subjects, however, no such evidence of reorganization may be observed [19,39], although more subtle differences using the correlation approach may be found that could reflect differences in the way the brain works during encoding. However, to the best of our knowledge the latter approach has never been applied to the study of aging, so more precise hypothesis cannot be generated at this stage.

## 2. Methods

### 2.1. Subjects

We studied twelve optimally healthy volunteers (six male and six female), of mean age 59 years (±2.5 S.D.; range: 55–63 years). All were healthy native French speakers and right-handed as determined by the Edinburgh Handedness Inventory (LQ = 95.58 ± 6.07). They were screened to rule out the presence of medical, psychiatric or neurological disorders. They all were un-medicated, had no memory complaint and had a normal T1- and T2-weighted magnetic resonance imaging (apart from changes expected with normal aging). All gave written informed consent prior to participation, and the research protocol was approved by the Regional Ethics Committee. The study was done in line with the Declaration of Helsinki. In order not to select old subjects with incipient dementia, they all obtained high scores on the Mattis Dementia Rating Scale (MADRS) (mean = 141.25 ± 2.9). This group was compared to the previously reported group of right-handed young subjects (mean age = 22.5 years ± 2.1; six male, six female; [4]); note that for this study, the overall PET data set was entirely reanalyzed using state-of-the-art processing software (see Section 2). Although, as anticipated, the older subjects (to be referred to as the old group below) had significantly less years of education than the younger subjects (to be referred to as the young group below), the two groups had equivalent vocabulary scores as estimated with the Mill Hill vocabulary test.

### 2.2. Experimental design

Each subject underwent 12 consecutive scans (injections of $H_2O^{15}$) during a single PET session lasting approximately 2 h and 30 min. Five different conditions, each replicated twice (except rest: four times), were performed in each scanning session. Each condition lasted a total of 2 min.

#### 2.2.1. Encoding

To highlight the brain areas specifically underlying intentional encoding, two tasks were contrasted: an intentional encoding task (target) in which subjects were explicitly instructed to read silently and memorize 24 words to be subsequently recalled, and a reading task (baseline) in which subjects were instructed to read silently 24 different words. In order to prevent as far as possible covert memorizing during the reading task, this condition was deliberately placed at the beginning of the scanning session, and the subjects were blinded to the fact that it involved memory, i.e., they were

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