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Abstract

Using PET, we have attempted to determine the neural substrates of age-related 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 analysed 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 frontal activation by additional frontal activation.

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 ten 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) 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 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, SD; 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 Methods). 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 hours and 30 minutes. Five different conditions, each replicated twice (except Rest: 4 times), were performed in each scanning session. Each condition lasted a total of 2 minutes.

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 told that they were taking part in a study about vocabulary. Acknowledging the risk of order effects, this choice was dictated by the constraints of our paradigm and represents the best possible compromise in attempting to control cognitive strategies [35]. In addition, to further prevent implicit memorizing, the subjects were instructed to count backwards by 3 following each scan involving the Reading condition, during 60 sec. Just before the Intentional Encoding task was to start, the subject was told that the instruction was in fact to memorize the words. During both conditions, the words were presented in lower case, sequentially on a computer screen for 4 seconds each, separated by a 1 second interstimulus interval. The four lists of words used in the Intentional Encoding and Reading conditions were matched for word frequency and word length (between 4 and 10 letters), and were counterbalanced across subject groups (i.e., Young and Old). To cancel out those brain regions involved in semantic processing in the subtraction analysis, subjects were instructed in both conditions to make a living/non-living judgement regarding each word, by pressing on one of two possible buttons of a response box. Half of the words presented referred to living objects.

2.2.2. Retrieval

To map the brain areas specifically underlying episodic retrieval, two conditions were contrasted: a Stem-Cued Recall task (target) and a Stem-Completion task (baseline). In the

Stem-Cued Recall task, subjects were instructed to recall aloud the words studied during the Intentional Encoding task. They were shown the 2 first letters of the words (bigrams), presented in random order. In the Stem-Completion task, subjects were shown bigrams different from those used during the Stem-Cued Recall task, and were instructed to say aloud the first word that came to mind beginning with the bigram shown. During each task, 24 bigrams (in lower case) were presented sequentially on a computer screen for 4 seconds, each separated by a 1 second interstimulus interval.

All stimuli were displayed in white against black background, on a monitor placed behind the tomograph. The stimuli were shown to the subject thanks to a mirror positioned above the head.

2.2.3. Rest

Subjects were instructed to relax, keep their eyes closed and not focus their mind on a precise thought. The Rest condition was only included to assess age-related changes in default-mode brain function [22]. The results will be reported elsewhere.

2.2.4. Scanning sequence

The requirement that the two Reading conditions come first in the scanning session (see above) constrained the scanning sequence to be used. The following scanning sequence was used: *Rest – Reading 1 – Reading 2 – Intentional Encoding 1 – Stem-Cued Recall 1 – Stem Completion 1 – Rest – Intentional Encoding 2 – Stem-Cued recall 2 – Stem Completion 2 – Rest – Rest.*

2.3. PET data collection

Subjects were scanned while lying supine in a dimly lit and quiet room. A black tent was set up around the tomograph to ensure total darkness. The head was gently immobilized in a dedicated head-rest. Head position was aligned transaxially to the orbitomeatal line with a laser beam. Measurements of regional distribution of radioactivity were performed with an Siemens ECAT HR+ PET device with full 3D volume acquisition allowing the reconstruction of 63 planes (thickness: 2.4 mm; axial field-of-view: 158 mm; effective resolution ~ 4.2 mm in all directions). Transmission scans were obtained with a ^{68}Ge source prior to emission scans. For emission scans, about 7 mCi of H_2O^{15} were administered as a slow bolus in the left antecubital vein by means of an automated infusion pump. The duration of each scan was 90 seconds. Each experimental condition was started 30 seconds before data acquisition and continued until scan completion. This process was repeated for each of the 12 scans, for a total injected dose of ~80 mCi. The interval between injections was 7 minutes 40 seconds; the position of the head was controlled with the laser beam prior to each injection.

2.4. PET data analysis

All calculations and image transformations were performed on UNIX SYSTEM workstations. First, the 12 scans of each subject were realigned to each other, using the AIR 3.0 software [46]. For subsequent data analysis, the Statistical Parametric Mapping software (SPM2, Welcome department of Cognitive Neurology, UK) implemented in the MATLAB environment was used. The images were non-linearly transformed into standard space (MNI template)[11] and smoothed using a 12 mm Gaussian filter. The images were scaled to an overall CBF grand mean of 50 ml/100g/min; we therefore refer to ‘adjusted rCBF’ in what follows. We used a gray matter threshold of 80% of the whole brain mean; and covariates were centred before inclusion in the design matrix.

The first analysis was designed to determine the activations common to the two groups of subjects and those specific to the Old as compared to the Young group. To this end, we used a Conjunction/Difference analysis in SPM2. The contrasts were between Intentional Encoding and Reading, and between Stem-Cued Recall and Stem Completion. An ANCOVA (analysis of covariance), using global activity as a confounding covariate, was performed on a voxel-by-voxel basis. These contrasts produced statistical parametric maps (SPMs) of the t statistic at each voxel. The results of t statistic (SPM {t}) were then transformed into a normal standard distribution (SPM {*Z*). For the common activations, contrasts were thresholded at a *P* value corresponding to 5% false discovery rate (FDR) to control for multiple comparisons [18]. Direct between-group comparisons contrasted [Intentional Encoding minus Reading]$_{Young}$ *versus* [Intentional Encoding minus Reading]$_{Old}$, and [Stem-Cued Recall minus Stem Completion]$_{Young}$ *versus* [Stem-Cued Recall minus Stem Completion]$_{Old}$. The significance cut-off was set at $P<0.05$, FDR corrected for multiple comparisons. Only activation clusters with size larger than 15 voxels were considered.

The second analysis was designed to compare the brain regions predictive of subsequent recall performance between the two groups of subjects. To this end, voxel-based correlations between rCBF obtained during Intentional Encoding (mean-adjusted rCBF from the 2 Intentional Encoding scans) and performance during Stem-Cued Recall (mean of the scores for the 2 Stem-Cued Recall scans) were first performed for each group separately. These contrasts produced statistical parametric maps (SPMs) of the t statistic at each voxel. The results of t statistic (SPM {t}) were then transformed into a normal standard distribution (SPM {Z}). The significance cut-off was set at $P<0.001$ (uncorrected). We only considered clusters larger than 15 voxels. In order to directly compare the correlations between the Young and Old groups, the adjusted rCBF values for the significant clusters from each within-group SPM correlation analysis were obtained by applying a spherical region of

interest (radius = 5mm) centred on the peak coordinates of each of the particular clusters, and the correlation coefficients were computed for each group separately and compared between the two groups according to standard statistical methods.

3. Results

3.1. Behavioral data

The behavioral results are shown in **Table 1**. There was no significant difference between Young and Old groups in living/non-living judgement performance for the Intentional Encoding and Reading conditions. The ANOVA on the Stem-Cued Recall performance scores showed a significant effect of age ($F = 11.89$, $P = 0.0023$) at the expense of the Old group. As expected, there was no difference between the two groups in performance during Stem Completion.

INSERT TABLE 1 ABOUT HERE

3.2. Imaging data

3.2.1. Intentional Encoding minus Reading

The findings are presented in **Table 2** and illustrated in **Figure 1**. Common activations were found in four distinct clusters, which involved the frontal operculum (BA 44/45), frontal pole (BA 10), dorsolateral prefrontal cortex (BA 9/46) and precentral gyrus (BA 6) on the left side; and the dorsolateral prefrontal cortex (BA 10 and 9/46) on the right side.

The direct between-group comparison showed no significant difference for either contrast (i.e., Young>Old and Old>Young).

INSERT TABLE 2 AND FIGURE 1 ABOUT HERE

3.2.2. Stem-Cued Recall minus Stem Completion

Common activations involved a large right dorsolateral prefrontal cluster (BA 10/46 and BA 9). See **Table 2** and **Figure 1**.

The direct between-group comparison showed no significant difference.

3.2.3. Correlation between rCBF during Intentional Encoding and performance during Stem-Cued Recall

In the Old group, significant clusters were located in the right inferior frontal gyrus (BA 44/45) and the left hippocampus (see **Table 3** for details). In the Young group, as previously reported [4], a large cluster centred in the left parahippocampal gyrus (BA 35/36).

INSERT TABLE 3 ABOUT HERE

The direct comparison of correlation results revealed no significant ($P<0.05$) between-group difference for either the left parahippocampal gyrus or the left hippocampus. However, there was a significant difference regarding the right inferior frontal gyrus ($P<0.001$), the correlation being significantly stronger in the Old as compared to the Young group (see **Figure 2**).

INSERT FIGURE 2 ABOUT HERE

4. Discussion

Below we will discuss firstly our findings in relation to intentional encoding, then the findings related to episodic retrieval, and finally the results of the correlation analysis, in relation with the behavioral data.

4.1. Intentional encoding

The pattern of activation common to both young and old subjects associated with intentional encoding of verbal stimuli was exclusively located in frontal regions, including Broca's area, the dorsolateral prefrontal cortex and the frontal pole bilaterally. The activation of Broca's area is unsurprising and would reflect the use of a rote rehearsal strategy in order to intentionally learn the lists of words [25]. The role of the dorsolateral prefrontal region in working memory/attentional processes is now well established [42]. These processes are in fact often associated with intentional episodic encoding and would be involved in the temporary maintenance/manipulation of the words to be remembered. Also, our intentional encoding task can be considered a dual task since participants were asked to make a semantic judgement while trying to learn the words. Dual tasks require added attentional cost, which could perhaps partly account for the observed differential recruitment of dorsolateral frontal regions bilaterally. It has been shown that the frontal pole is involved in updating processes [45]. According to Fletcher and Henson [17], this region would be associated with higher order function such as the management of sub-processes or sub-goals in the setting of memory tasks, which in the present paradigm would include rote rehearsal, maintenance/manipulation of the words, and semantic decision.

The absence of significant difference between young and old subjects suggests that both groups activated the same task-related or state-related network during the Intentional

Encoding task. Logan and colleagues recently highlighted an age-related difference of activation in a specific left prefrontal region (Brodmann area 45/47) during intentional encoding of words by comparison to a fixation condition [29]. This region is usually associated with semantic processing (see [7] for review) and since subjects were only instructed to intentionally encode the words, the age-related difference is likely to reflect a differential use of spontaneous semantic elaboration. In our study, we controlled both Intentional Encoding and its baseline (Reading condition) for semantic processing, which probably explains why we found no activation or between-group difference in this very specific region. Although the level of processing is a better factor than intentionality for modulating memory performance, there are also strong interactions between these two factors, dictating caution when manipulating them. Subjects are likely to use a rote rehearsal strategy during an intentional encoding condition whereas this should not be the case during incidental encoding. Rote rehearsal may not be as efficient as semantic processing for the efficient encoding of words, but the combination of both is more efficient than the latter alone. Moreover, when comparing groups like young and old, it is important to ensure that both use same strategies during the memory tasks and that any age-related difference in brain activity is unlikely to be related with the use of different strategies, which could occur when factors such as intentionality and level of processing are not properly controlled.

However, the subtraction analysis shows only the regions "involved" in Intentional Encoding in both groups but does not address the issue of the efficiency of this encoding. The results obtained with the correlation analysis might give us better clues regarding this issue (see below).

4.2. Episodic retrieval

The activation associated with episodic retrieval of words regardless of age involved the right prefrontal cortex. This finding fits well with the HERA (hemispheric encoding/retrieval asymmetry) model according to which the right prefrontal cortex is preferentially involved in episodic retrieval [43] and is in agreement with the results reported in previous studies in which there was no noticeable age-related difference regarding activations in the right prefrontal region during episodic retrieval (e.g. [1, 10, 19, 39, 41]. More precisely, it has been suggested that this region may be involved in "retrieval mode", a neurocognitive state in which subjects maintain an attentional focus on a particular past episode during retrieval [27]. This hypothesis is particularly attractive with respect to our study because it posits that the regions involved in retrieval mode are activated regardless of the efficacy of retrieval, and hence would explain why we found a significant age-related decline in retrieval scores but no significant between-group difference in right frontal activation. However, based on a comprehensive meta-analysis, Cabeza [9] proposed a model, termed "hemispheric asymmetry reduction in older adults" or HAROLD, according to which prefrontal activity during episodic memory would become less lateralized with increasing age, reflecting compensatory or "dedifferentiation" processes. Thus, according to this model, a more bilateral frontal activation would be expected in older subjects, but we did not observe this. Our results can however be explained by taking into account the results of a study by Cabeza and collaborators [8], where three different groups of subjects (younger subjects, low-performing older subjects, high-performing older subjects) were scanned while performing an episodic retrieval task of verbal material. While younger and low-performing older subjects recruited similar right prefrontal regions, high-performing older subjects engaged prefrontal regions bilaterally. Thus, low-performing older adults recruited a similar network as young adults but used it inefficiently, whereas high-performing older adults counteracted age-related neural decline through a reorganization of neurocognitive networks, resulting in a bilateral

activation. Our finding of a lack of bilateral activation in the face of reduced behavioral performance would therefore be consistent with this earlier study. A potential extension of our work would be to compare (using the same principle as in [8,13,37]) high- and low-performing subjects with our episodic retrieval task, with the hypothesis that high-performing old subjects engage a bilateral frontal network. However, there are some important differences between our study and that of Cabeza and collaborators regarding the fact that subjects of our study are much younger than those described in Cabeza et al's study and that the young and old subjects in the present report have overlapping performance distributions, whereas Cabeza et al's subjects were completely separated by .5 SD. Interpretation of our results therefore remains somewhat speculative.

There are two main reasons for which we decided to put the stem-recall task before the stem completion task in our paradigm. Firstly, we believe that interactions regarding the strategies used are not as strong between these two kinds of tasks as they can be between incidental and intentional encoding conditions. And secondly, our stem-cued recall task is a difficult task, especially for older subjects, and preliminary behavioural data obtained in a pilot study showed that using the stem-completion task before the stem-cued recall generates a significant decrease of episodic memory performance, with some older subjects being at floor level.

4.3. Regions predictive of subsequent memory performance

The most salient result obtained from the correlation analysis between rCBF during Intentional Encoding and performance during Stem-Cued Recall concerned the left medial temporal region – more precisely the parahippocampal region in young subjects and the hippocampus proper in older subjects. Thus, in both groups neural activity in the left hippocampal region during encoding was highly predictive of subsequent retrieval success,

i.e. the higher the activity in this region during encoding, the better the recall performance. This finding is consistent with previous PET and fMRI scan/performance correlative studies [16,26], as well as with event-related fMRI in young subjects [33].

We found no significant between-group difference in the correlation between rCBF and retrieval scores for the left medial temporal region. This suggests that normal aging does not affect the role of this region in mediating encoding success. This finding is consistent with other recent studies [5,32] that also show that, regardless of age, the degree of activity in the medial temporal regions during encoding correlates with subsequent retrieval performance (although an age-related difference in hippocampal region activation has been reported [13,24]). This in turn suggests that the expected histopathological counterparts of normal aging in this region, especially neurofibrillary degeneration whose incidence increases from 20% in 50-55-year-olds to 80% in 55-year-olds and over [31] and affect 100% of subjects over 75 yrs of age [14], may not substantially compromise its function in terms of encoding success. Although studying even older subjects could have shown different results, it is well known that it is almost impossible to recruit strictly healthy and unmedicated volunteers older than 65 years, yet optimal health is a requirement in functional neuroimaging studies of normal aging to avoid confounders such as medication, small vascular lesions and incipient dementia [3].

We found a significant ($P<0.005$) between-group difference in the right inferior frontal gyrus correlation, which was significant in older but not in young subjects. The data indicate that in the young group activity in this region was unrelated to retrieval performance, while in the older subjects, it was positively correlated such that the better the performance the higher the activity. Since there was no significant difference between the two groups in this area in the conjunction analysis, the findings would not support a difference in cognitive effort across the

group. Since the older subjects obtained significantly lower retrieval performance than the young, one possible interpretation for the difference in activity-performance correlation would involve functional reorganization of the encoding network. In other words, the less efficient encoding might be mediated by less "specific" or "focused" brain activity including not only the left medial temporal region, as in young subjects, but also the right inferior frontal gyrus as a compensatory process. Interpretation of our results regarding this brain region should be considered with caution because of the small samples and different ranges of values, and could be due to chance. However, a non-parametric analysis using Spearman rank correlation confirmed the significant age-related difference in this region ($P<0.005$, with and without the Young outlier, respectively), which suggests the finding is robust.

The results from this study therefore serve to illustrate that apart from the classic finding of more widespread and bilateral activations in the face of maintained performance, age-related cerebral reorganization can, in the case of reduced performance, express itself as unchanged cerebral activation pattern but subtle differences in the correlation between local perfusion and performance, eluded by classic activation mapping.

In conclusion, this PET study using combined subtraction/correlation analysis suggests that the lower performance exhibited by older subjects during an effortful episodic retrieval task is due to a combination of i) a subtle encoding deficit associated with a more widespread pattern of correlations between rCBF during encoding and subsequent retrieval performance; and ii) a less efficient retrieval network, evidenced by unaltered activation pattern despite reduced performance, suggesting the aged brain is unable to compensate for reduced efficiency of right frontal activation by additional left frontal activation. This inadequacy to compensate for age-related brain changes translates as a selective cognitive decline.

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Figure legends

Figure 1

Significant common activations (thresholded at $P<0.05$, FDR-corrected for multiple comparisons) rendered onto the canonical T1-weighted brain MRI surface of SPM2. **A**: Intentional Encoding *minus* Reading; **B**: Stem-Cued Recall *minus* Stem Completion

Figure 2

Areas where rCBF during Intentional Encoding was significantly correlated with retrieval performance in the Young (A: Left parahippocampal gyrus) and Old (B: Left hippocampus, C: Right inferior frontal gyrus) groups. The correlations were not significantly different between the two groups for (A) (Young: r = 0.88; Old: r = 0.52) and (B) (Young: r = 0.63; Old: r = 0.86). However, the correlation for (C) (Young: r = 0.17; Old: r = 0.94) was significantly stronger in the Old as compared to the Young group ($P<0.001$; still significant if the outlier from the Young group, below right, is removed).

Table 1. Mean percent scores for the semantic decision task (living/non-living) during the Intentional Encoding and Reading conditions, and for the Stem-cued recall and Stem completion tasks (SDs in parentheses)

	Younger subjects	Older subjects
Living/non-living	0.97 (±0.03)	0.97 (±0.03)
Stem-cued recall	0.57 (±0.09)	0.42 (±0.13)*
Stem completion	0.96 (±0.04)	0.96 (±0.04)

* $P < 0.005$

Table 2. Regions of significant rCBF increases ($P<0.05$, FDR-corrected for multiple comparisons). Coordinates of voxels of maximal activation refer to the stereotactic space provided by the Montreal Neurological Institute (MNI) brain (BA: approximate Brodmann area).

Cluster size (voxels)	Brain region	BA	Stereotactic coordinates			Z score
			x	y	z	
Intentional encoding versus Reading (young + old)						
457	Left middle frontal gyrus	10/46	-26	56	12	5.45
	Left superior frontal gyrus	10	-28	46	0	4.26
765	Left inferior frontal gyrus	44/45	-32	16	18	5.53
	Left middle frontal gyrus	9/46	-38	24	32	4.29
259	Right middle frontal gyrus	10	47	50	16	4.13
	Right middle frontal gyrus	9/46	44	32	28	3.90
	Right middle frontal gyrus	9/46	49	40	28	3.75
114	Left precentral gyrus	6	-36	-4	38	3.83
Stem-cued recall versus Stem completion (young + old)						
925	Right middle frontal gyrus	10	38	52	16	5.18
	Right middle frontal gyrus	10/46	38	44	22	5.05
	Right middle frontal gyrus	10	32	58	6	4.53
	Right middle frontal gyrus	9	38	32	34	3.88

Table 3. Positive correlations (P<0.001, uncorrected) between rCBF during Intentional Encoding and Stem-Cued Recall performance in the Old group. Coordinates of peak correlation voxels are shown (BA: approximate Brodmann area).

Cluster size (voxels)	Brain region	BA	Stereotactic coordinates			Z score
			x	y	z	
89	Right inferior frontal gyrus	44/45	36	18	21	4.56
64	Left hippocampus		-22	-16	-14	3.6