

Research report

# An fMRI study of the functional neuroanatomy of picture encoding in younger and older adults

Tetsuya Iidaka<sup>a,\*</sup>, Norihiro Sadato<sup>b</sup>, Hiroki Yamada<sup>c</sup>, Tetsuhito Murata<sup>d</sup>, Masao Omori<sup>d</sup>,  
Yoshiharu Yonekura<sup>a</sup>

<sup>a</sup>Biomedical Imaging Research Center, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Yoshida, Fukui, 910-1193, Japan

<sup>b</sup>National Institute for Physiological Sciences, Myodaiji, Okazaki, Aichi, 444-8585, Japan

<sup>c</sup>Department of Radiology, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Yoshida, Fukui, 910-1193, Japan

<sup>d</sup>Department of Neuropsychiatry, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Yoshida, Fukui, 910-1193, Japan

Accepted 22 August 2000

## Abstract

Age-related changes in the neural mechanisms of picture encoding were investigated using functional magnetic resonance imaging (fMRI). Seven younger and seven older adults were studied while they were encoding pairs of concrete-related, concrete-unrelated, and abstract pictures. Functional (T2\*-weighted) and anatomical (T1-weighted) images of the brain were obtained using a 1.5 T MRI scanner. The results in the younger adults showed that the left dorsal prefrontal cortex (PFC) was activated during associative learning of the concrete-unrelated or abstract pictures. The results also suggest that both ventral and dorsal visual pathways are involved in the encoding of abstract pictures, and that the right superior parietal lobule likely mediates spatial information of the abstract pictures. The older adults showed significant activation in the left dorsal PFC under concrete-unrelated and abstract conditions. However, the older adults failed to activate either the left ventral and right dorsal PFC under the concrete-unrelated condition, or the parietal areas under abstract condition. A direct comparison between the two age groups demonstrates that the older adults had a reduced activation in the bilateral parieto-temporo-occipital areas under abstract condition, and in the right temporo-occipital area extending to the fusiform gyrus under the concrete-unrelated condition. Finally, age difference was found in correlation between memory performance and amplitude of signal change in the parahippocampal gyrus and fusiform gyrus under the concrete-unrelated and abstract conditions. These changes in neural response likely underlie the age-related memory decline in relation to pictorial information. © 2001 Elsevier Science B.V. All rights reserved.

*Theme:* Neural basis of behavior

*Topic:* Aging

*Keywords:* Episodic memory; Parietal lobe; Concrete picture; Abstract picture; Neuroimaging; Aging

## 1. Introduction

Although studies in cognitive psychology show that old subjects have greater difficulty in encoding and recalling information than do younger subjects [11], the neural mechanisms underlying these declines are still unclear. Most work on age-related memory decrements has used verbal or spatial materials, but studies with pictorial materials also help to clarify the issue. Overall, the

memory of pictures is relatively well-preserved in older subjects and age-differences are small [11]. Experimental manipulation regarding contextual information and the concreteness of stimuli is necessary to clarify the age-related decline in picture memory. For example, Park et al. [33] have used line drawings of concrete object pairs (related and unrelated) as learning materials. The authors observed larger age differences in cued recall of unrelated pairs than in that of related pairs, and they concluded that the semantic associations between related objects acts as a memory support in older subjects. Smith et al. [39] have found significant age differences for abstract but not for concrete pictures, indicating that the lack of semantic elaboration reduces the performance of older subjects.

\*Corresponding author. School of Informatics and Sciences, Nagoya University, Nagoya, 464-8601, Japan. Tel.: +81-52-789-4883; fax: +81-52-789-4883.

E-mail address: iidaka@info.human.nagoya-u.ac.jp (T. Iidaka).

These results suggest that semantic information related to the stimuli facilitates later memory performance particularly in older adults, and that the brain regions related to the processing of non-verbal stimuli such as abstract pictures are vulnerable to aging.

Age-related changes in the neural substrates of memory have been investigated during encoding and retrieval of faces [16] and words [5,6,29] using positron emission tomography. In these studies, older adults have been found to have reduced activity in the frontal lobe [5,6,16], hippocampus [16], and temporo-parieto-occipital lobe [5,6,16] during encoding. Grady et al. [19] reported that young subjects significantly activated the right medial temporal lobe during picture encoding, but older subjects did not. Grady et al. [18] also reported that older subjects have less activation in the left ventral prefrontal cortex during a face working memory task. Together, these studies suggest that the poorer memory performance of older adults results, in part, from insufficient encoding operations mediated by multiple brain regions.

In the present study, fMRI was obtained during the encoding of pairs of concrete (related and unrelated) or abstract pictures in younger and older adults. The first aim of the study was to investigate the neural correlates of picture encoding using concrete and abstract materials in younger adults. The superiority of memory performance for pictures compared to that for words has been attributed to people being more likely to store in their memory both a visual and verbal representation of pictures [34]. As reported by Park et al. [33] and Smith et al. [39], effective processing of verbal representation of picture may facilitate later memory performance. The differences in the encoding operations between concrete and abstract pictures are likely to be reflected in neural responses, and therefore detected by functional brain imaging. Our prediction was that the prefrontal cortex (PFC), ventral temporal, and parietal cortices would be activated during picture encoding [24,27], however, the pattern of activation in each hemisphere and in ventral/dorsal visual pathways [44] would be different depending on the types of materials to be learned.

The second, but major, aim of the study was to elucidate age-related differences in the neural mechanisms of picture encoding. We expected that the manipulations of the semantic relation and concreteness of pictures in the experimental design would elucidate the nature of age differences in pictorial memory. Particularly, as evidenced by Smith et al. [39], the lack of verbal support in the encoding of abstract pictures would result in inferior performance for older adults. A PET study by Ricci et al. [36] showed significant activation in the bilateral inferior temporal lobe during semantic association tasks of real objects. It is predicted that encoding of concrete pictures would involve the ventral part of the temporal lobe, and the older adult would show less activation in this region. In addition, age difference would be greater under the con-

crete-unrelated condition than under the concrete-related condition because the older adult's memory is particularly sensitive to semantic associations between pictures [33]. Finally, we expected that greater visuospatial attention would be required under the abstract condition than under the concrete conditions. Several authors [9,10] reported that the parietal lobe played a role in memory and attention of spatial information. Therefore, the older adults who had difficulty in memorizing abstract pictures as shown by Smith et al. [39] would show less activation in those areas related to the processing of spatial information.

## 2. Materials and methods

### 2.1. Subjects

Seven younger and seven older subjects participated in the study after giving written informed consent. The subjects were community-dwelling, healthy, and independent-living adults. The subjects' physical health was verified in an interview before the study, and those who had a history of neurological, psychiatric, or physical diseases were excluded from the study. No subject was taking drugs that could affect the cerebral blood flow. No older adult had incidental cerebral infarctions or high-density areas in the deep white matter defined by T2-weighted images of the brain. Except for one older adult who was ambidextrous, all subjects were strongly right-handed (assessed by the Edinburgh Handedness Inventory). The younger adults had significantly more years of education than did the older adults. Before the experiment, neuropsychological tests and a shorter version of the experimental task were administered to confirm that subjects could perform at an average level. The younger adults outperformed the old adults in trail making A, digit symbol, and cued recall of words (Wechsler Memory Scale), but the result for the immediate recall of figures (Wechsler Memory Scale) did not differ between the groups. The demographic characteristics and neuropsychological performance for the group are shown in Table 1. This study was approved by the ethics committee at Fukui Medical University.

### 2.2. Task procedure

The objects for the picture-encoding task were taken from the line drawings of Snodgrass et al. [41] and Nishimoto et al. [31]. In a pilot study, 150 pictures with a high rate of agreement (more than 80%) in naming were selected from the drawings by Snodgrass et al. [41] for use as concrete pictures. Thirty-two pairs of concrete-related pictures were created by coupling objects that were semantically associated with each other (e.g., coat and hanger, toaster and bread, ashtray and cigarette, Fig. 1, left). Thirty-two pairs of concrete-unrelated pictures were

Table 1  
Demographic characteristics and neuropsychological performance<sup>a</sup>

	Young adults	Older adults	
N (M/F)	7 (4/3)	7 (4/3)	
Age (years)	25.7 (3.8)	66.2 (4.9)	
Education (years)	17.1 (0.6)	15.4 (1.5)	*
Trail making A (s)	20 (5.6)	35.7 (8.4)	**
Digit symbol	80.1 (13.9)	53.8 (7.4)	**
Word recall (WMS)	20.2 (0.9)	16.9 (2.6)	**
Figure recall (WMS)	13.7 (0.4)	12.7 (1.4)	n.s.

<sup>a</sup> M, Male; F, Female; WMS, Wechsler Memory Scale. The results of one-way ANOVA are shown in the right-hand column. \* $P < 0.05$ ; \*\* $P < 0.01$ ; n.s., not significant.

created by coupling objects with no or little association (e.g., giraffe and doorknob, bed and button, alligator and piano, Fig. 1, middle). The proportion of living/non-living objects and the mean frequency of the objects' names were matched between groups of related and unrelated pairs. For abstract pictures, we used nonsense objects created and standardized by Nishimoto et al. (Fig. 1, right) [31]. The set of abstract pictures was similar to those used by Bower et al. [2].

Four lists of eight pairs each were created for each condition. One list of each type of condition was assigned to each of the experimental blocks. Within each block, pairs were successively presented at a rate of 6 s/pair (4.5 s duration and 1.5 s cross hair inter-stimulus interval). Subjects were instructed to memorize the pairs for a subsequent recognition test by making meaningful associations between pictures, or by paying attention to the similarity of the objects' shapes. No overt response was required during the encoding task. During a control condition, visual noise patterns were presented, and the subjects were told to watch them without thinking about the pictures presented before. Hence, there were three task conditions (concrete-related, CR; concrete-unrelated, CU; and abstract, AB) and one control condition. The order of the three task conditions was counterbalanced within and across subjects.

Memory performance for the pictures was tested by a post-scan recognition test. In this test, half of the pairs presented during the experiment were used. A testing sheet with randomly arrayed pictures in two columns was presented to the subjects. Subjects were told to draw lines

to connect correct pairs learned during the experiment. The proportion of correct answers was subjected to a two-way ANOVA with the condition (CR×CU×AB) and age (younger×older) as factors.

### 2.3. fMRI procedure and data analysis

For each subject, functional (T2\*-weighted) images, followed by an anatomical (T1-weighted) image, were acquired with a 1.5 Tesla MRI scanner (GE, Milwaukee, WI, USA). In the older adults, T2-weighted images were also acquired in order to exclude those who had incidental cerebral infarctions or high-density areas in the deep white matter. Functional images consisted of echo-planar image volumes that were sensitive to BOLD contrast in axial orientation (TR=6000 ms, TE=40 ms, flip angle=90). Prior to each run, four discarded volumes were acquired to allow for a stabilization of magnetization. The volume covered the whole brain with a 64×64 matrix and 24 slices (voxel size=3.75×3.75×6 mm, slice thickness=5 mm, gap=1 mm). A run of 128 image volumes with 32 volumes in each of the four conditions was performed. The successive functional images for each subject were realigned to the final image, normalized to Talairach and Tournoux [43] standard space, and spatially smoothed with a 10 mm Gaussian kernel using SPM96 (Wellcome Department of Cognitive Neurology, London, UK). Significant hemodynamic changes for each contrast specified by the design matrix were assessed using *t*-statistics on a voxel-by-voxel basis [13].

In the group analysis, the repeated measures of the BOLD signal were collapsed within subjects (adjusting for both global signal by using proportional scaling and for low-frequency physiological drifts by using a high-pass filter) to give one scan per condition per subject according to the random effect model [10,14]. In the present study, the activation data were analyzed by subtracting the control condition from the CR, CU, or AB condition and by making subtractions between task conditions. The significance of these subtractive analyses was assessed by comparing the expected and observed distribution of the *t*-statistic under the null hypothesis of no activation effect on MRI signal [13]. According to previous studies using SPM (e.g. [37]), we report activation above a threshold

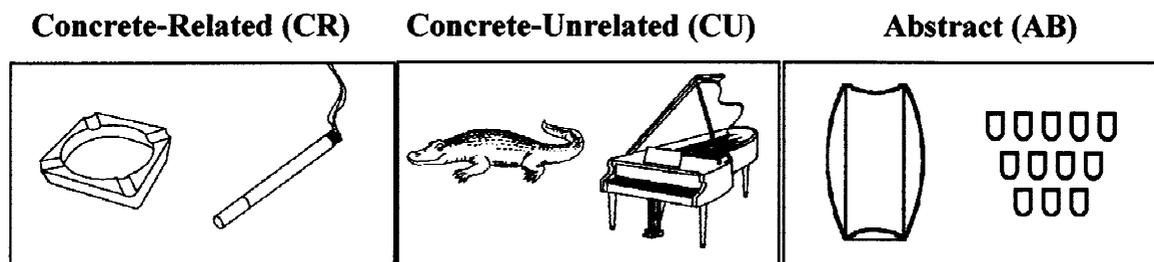


Fig. 1. Examples of pairs of concrete-related (left), concrete-unrelated (middle), and abstract (right) pictures.

corresponding to  $P=0.001$  (uncorrected for multiple comparison,  $Z=3.09$ ) for height in the group analysis for each of the younger and older adults. Empirically, this threshold has been shown to guard against the excessive occurrence of false-positive errors. Areas that survived multiple comparison ( $P<0.05$ ) are indicated by an asterisk. For the between-group analysis, activated voxels above  $P=0.005$  (uncorrected,  $Z=2.58$ ) for height were reported. The statistical threshold for extent was set to  $P=0.05$  (uncorrected). The results from the between-group analysis can be ascribed either to activation in one group or to deactivation in the other. To avoid the potential contribution of deactivation in one group, the results were masked by activations in the corresponding subtraction for both groups.

To investigate relationship between memory performance and signal change, the proportion of correct answers in each subject and condition was entered into correlation analysis as covariate. The group-specific regressions at every voxel were computed to test the differences between the regression slopes for the younger and older groups. The resulting SPM demonstrates the significant group-specific changes in the contribution of memory performance to amplitude of signal changes during the task condition as compared to the control condition. In the present study, those areas with positive correlation in the younger adults and with no correlation in the older adults are investigated. The statistical threshold was set to  $P=0.005$  (uncorrected) for height and to  $P=0.05$  (uncorrected) for extent. The

proportion of correct answers and signal change in each subject are plotted in the figures.

### 3. Results

#### 3.1. Behavioural data

The mean (S.D. in parentheses) proportions of correct answers in the memory test for the younger adults were 0.98 (0.03), 0.72 (0.25), and 0.64 (0.26) under the CR, CU, and AB conditions, respectively. The older adults' memory performance was 0.89 (0.1), 0.44 (0.31), and 0.33 (0.22) under the CR, CU, and AB conditions, respectively. The results of two-way ANOVA showed significant main effects of age ( $F=10.8$ ,  $P<0.01$ ) and condition ( $F=15.8$ ,  $P<0.01$ ), but there was no significant interaction ( $F=1.0$ ,  $P>0.3$ ).

#### 3.2. fMRI data

##### 3.2.1. Younger adults

The locations and peak values of significant activation relative to the control condition in the younger adults are listed in Table 2A–C. These clusters are superimposed on a normalized high-resolution T1 image of a single subject (Fig. 2). Under the CR condition, only the bilateral occipito-temporal areas show significant activation (Fig. 2, left). Similar activity in the extrastriate cortex was found

Table 2  
Locations and peak values of activation: young adults<sup>a</sup>

	L/R	Region name	(BA)	<i>x,y,z</i>	<i>Z</i>
(A) Concrete-related minus Control	L	inf. occipital gy.	(18)	-38,-80,-2	5.28*
	R	fusiform gy.	(37)	38,-60,-24	5.91*
(B) Concrete-unrelated minus Control	L	inf. occipital gy.	(18)	-38,-80,-2	5.23*
	R	fusiform gy.	(37)	38,-60,-24	6.9*
	L	inf. frontal gy.	(46)	-48,30,22	5.26*
	R	mid. frontal gy.	(46)	56,36,16	3.97
	L	inf. frontal gy.	(47)	-48,28,-8	4.09
	L	sup. parietal lob.	(7)	-34,-56,54	4.02
	L	sup. frontal gy.	(6)	-8,16,62	4.14
(C) Abstract minus Control	L	inf. occipital gy.	(18)	-38,-80,0	6.18*
	L	sup. parietal lob.	(7)	-34,-56,54	4.78*
	R	fusiform gy.	(37)	38,-60,-24	6.77*
	R	sup. parietal lob.	(7)	28,-56,44	4.72*
	L	inf. frontal gy.	(46)	-48,30,22	5.33*
	R	mid. frontal gy.	(9/44)	56,16,28	4.6*
	L	inf. parietal lob.	(40)	-44,-30,40	4.57
(D) Concrete-unrelated minus Concrete-related	L	sup. frontal gy.	(6)	-22,8,50	4.17
	L	mid. frontal gy.	(46)	-50,30,22	4.08
(E) Concrete-related minus Concrete-unrelated	L	post. cingulate gy.	(23)	-6,-32,24	4.15
(F) Abstract minus Concrete-related	L	mid. frontal gy.	(46)	-50,32,22	4.2
	R	sup. parietal lob.	(7)	28,-56,44	3.85
	L	post. central gy.		-60,-24,42	4.01
	R	mid. occipital gy.	(19)	42,-80,12	3.76
(G) Concrete-related minus Abstract	R	precuneus	(7)	10,-50,32	4.62*
	R	sup. temporal gy.	(22)	56,-56,18	4.3

<sup>a</sup> \*corrected threshold at  $P=0.05$ . inf, inferior; mid., middle; sup., superior; post, posterior; gy., gyrus; lob., lobule.

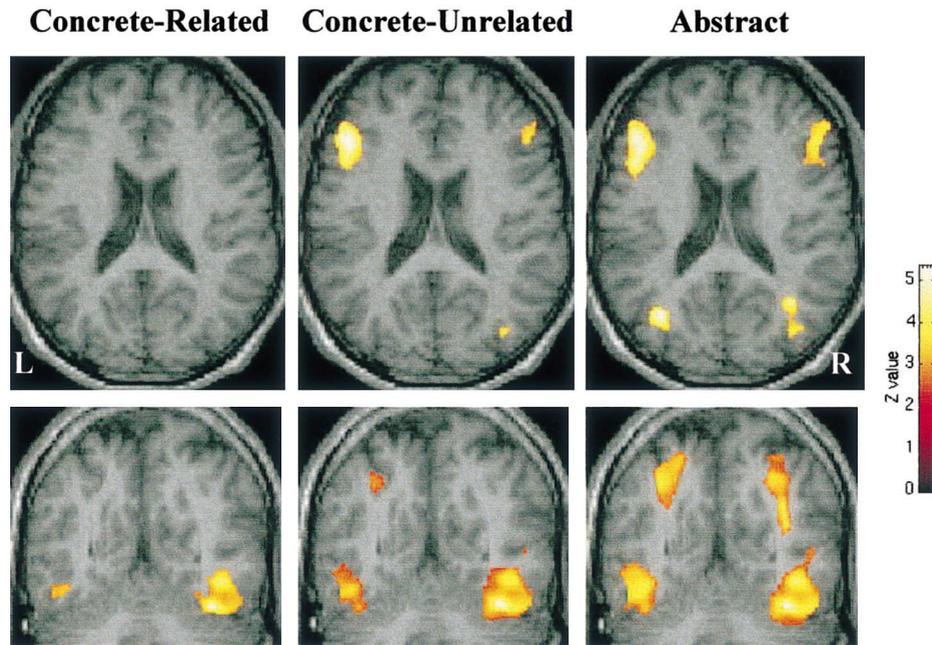


Fig. 2. Activated regions in the subtraction of the control condition from the concrete-related (left), concrete-unrelated (middle), and abstract (right) conditions are superimposed on a normalized T1 image of a single younger subject. The statistical threshold was set at  $P=0.001$ , uncorrected ( $Z=3.09$ ). Transverse images (first row) at  $z=20$  mm and coronal images (second row) at  $y=-60$  mm in coordinates by Talairach and Tournoux are shown. The coordinates are listed in Table 2.

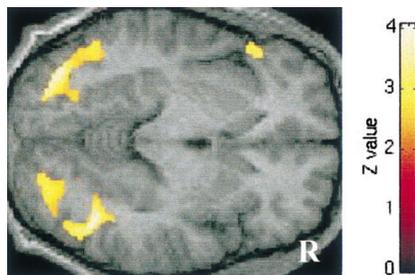


Fig. 3. Activated regions in the subtraction of the control condition from the concrete-unrelated condition are superimposed on a normalized T1 images of a single younger subject. Activity in the left ventral prefrontal cortex (BA47) and temporo-occipital lobe is shown. The coordinates are listed in Table 2B. The statistical threshold was set at  $P=0.001$ , uncorrected ( $Z=3.09$ ).

both under the CU and AB conditions. Under the CU condition, activation in the dorsal prefrontal cortex (PFC) was bilateral (Fig. 2, middle), whereas that in the superior parietal lobule (SPL) and ventral PFC (Fig. 3) was left-lateralized. Under the CU condition, there was also activity in the medial part of the frontal lobe. The encoding of abstract pictures strongly activated the bilateral PFC, SPL (Fig. 2, right), and left inferior parietal lobule. Finally, activation in the left lateral premotor area was involved under the AB condition.

The results for the subtractions between conditions in the younger adults are shown in Table 2D–G. There was a significantly greater signal under the CU than under the CR condition in the left dorsal PFC (Fig. 4, left). Signals in the left PFC, right SPL, and occipital areas were greater

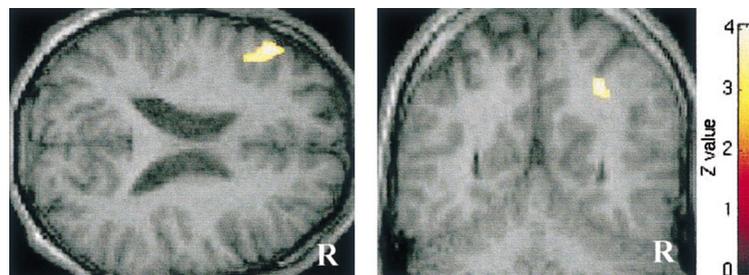


Fig. 4. Left: Activated region in the subtraction of the concrete-related condition from the concrete-unrelated condition. Activity in the left dorsal prefrontal cortex is shown. The coordinate is listed in Table 2D. Right: Activity in the right intraparietal sulcus in the subtraction of the concrete-related condition from the abstract condition. The coordinate is listed in Table 2F. The statistical threshold was set at  $P=0.001$ , uncorrected ( $Z=3.09$ ).

Table 3

Locations and peak values of activation: older adults<sup>a</sup>

	L/R	Region name	(BA)	<i>x,y,z</i>	Z
(A) Concrete-related minus Control	L	mid. occipital gy.	(19)	-38,-80,-10	5.37*
	R	inf. occipital gy.	(18)	30,-86,-2	4.82*
	L	fusiform gy.	(37)	-34,-80,-30	4.67
	R	fusiform gy.	(37)	40,-48,-30	4.53
(B) Concrete-unrelated minus Control	L	mid. occipital gy.	(19)	-38,-80,-10	6.12*
	R	inf. occipital gy.	(18)	30,-86,-2	5.52*
	R	fusiform gy.	(37)	40,-50,-30	5.08*
		sup. frontal gy.	(6)	-2,16,54	4.78*
	L	inf. frontal gy.	(46)	-44,30,22	4.49
	L	sup. frontal gy.	(6)	-34,18,60	3.8
(C) Abstract minus Control	L	inf. occipital gy.	(19)	-38,-80,-12	6.05*
	R	fusiform gy.	(37)	40,-80,-28	5.41*
	R	inf. occipital gy.	(18)	30,-86,-2	5.15*
	L	sup. parietal lob.	(7)	-24,-68,52	4.68
	L	inf. frontal gy.	(46)	-42,32,22	4.56
		sup. frontal gy.	(6)	6,18,58	4.34
		cerebellum		6,-78,-38	3.97
	L	sup. frontal gy.	(6)	-38,12,60	3.78

<sup>a</sup> For abbreviations see Table 1 legend.

under the AB than under the CR condition. Particularly in the right parietal area, peak activity was identified in the depths of the intraparietal sulcus (Fig. 4, right).

### 3.2.2. Older adults

The locations and peak values of significant activation for the older adults are listed in Table 3. These clusters are superimposed on a normalized high-resolution T1 image of

a single older adult (Fig. 5). The older adults activated bilateral temporo-occipital areas under the three experimental conditions. Under the CU condition, the older adults showed significantly greater signals relative to the control condition in the left dorsal prefrontal cortex (Fig. 5, middle). During the encoding of abstract pictures (Fig. 5, right), significant activation was found in the left dorsal PFC and SPL. Medial and lateral premotor areas were

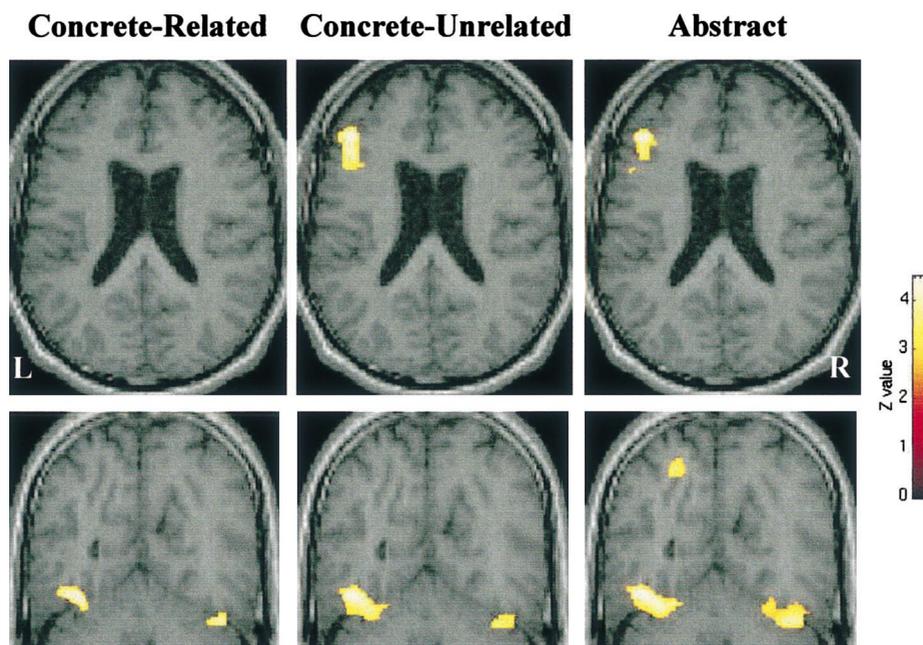


Fig. 5. Activated regions in the subtraction of the control condition from the concrete-related (left), concrete-unrelated (middle), and abstract (right) conditions are superimposed on normalized T1 images of a single older subject. Transverse images (first row) at  $z=20$  mm, and coronal images (second row) at  $y=-64$  mm in coordinates by Talairach and Tournoux are shown. The coordinates are listed in Table 3.

Table 4  
Locations and peak values of activation: young vs. older adults<sup>a</sup>

	L/R	Region name	(BA)	<i>x,y,z</i>	Z
(A) Concrete-related minus Control: Young>Older	No significant voxel				
(B) Concrete-unrelated minus Control: Young>Older	R	mid. occipital gy.	(19)	48, -70, 2	4.57
	R	fusiform gy.	(37)	46, -50, -16	3.59
(C) Abstract minus Control: Young>Older	L	mid. temporal gy.	(39)	-34, -70, 20	4.39
	L	sup. parietal lob.	(7)	-32, -56, 52	3.69
	L	inf. temporal gy.	(37)	-52, -48, -12	3.59
	L	inf. parietal lob.	(40)	-52, -26, 42	3.68
	R	mid. occipital gy.	(19)	38, -74, 8	4.96
	R	inf. temporal gy.	(37)	48, -50, -14	4.27
	R	inf. parietal lob.	(40)	40, -54, 44	3.76

<sup>a</sup> For abbreviations see Table 1 legend.

activated under both the CU and AB conditions. There was no significant activation in the subtraction between conditions.

### 3.2.3. Between-group analysis

A direct comparison between the younger and older adults yielded significant differences in activation for only the CU and AB conditions (Table 4 and Fig. 6). Overall, the younger adults activated the occipito-temporo-parietal cortices more than did the older adults. By contrast, there was no region in which the signal increase was greater in the older than younger adults under any of the three conditions. Under the CU condition, age-related differences in activation were found in the right occipito-temporal areas extending to the anterior part of the fusiform gyrus (Fig. 6, left). During the encoding of abstract pictures, the younger adults activated the bilateral inferior temporal gyrus, superior and inferior parietal lobule, and occipital lobe more than did the older adults (Fig. 6, right).

### 3.2.4. Correlation analysis

A slope of regression line between memory performance and signal change in the left parahippocampal gyrus (Fig. 7a) and the right middle frontal gyrus ( $x,y,z=30,24,26$ ) under the CU condition had a significant age difference. There were significant age differences in regression slopes between memory performance and signal change in the right fusiform gyrus (Fig. 7b), right middle frontal gyrus ( $x,y,z=34,44,-12$ ) and left inferior temporal gyrus ( $x,y,z=-48,-16,-18$ ) under the AB condition.

## 4. Discussion

### 4.1. Activation in younger adults

One of the purposes of the present study was to examine the neural substrates of picture encoding in normal younger subjects. The bilateral dorsal PFC was activated during the encoding of concrete-unrelated and abstract

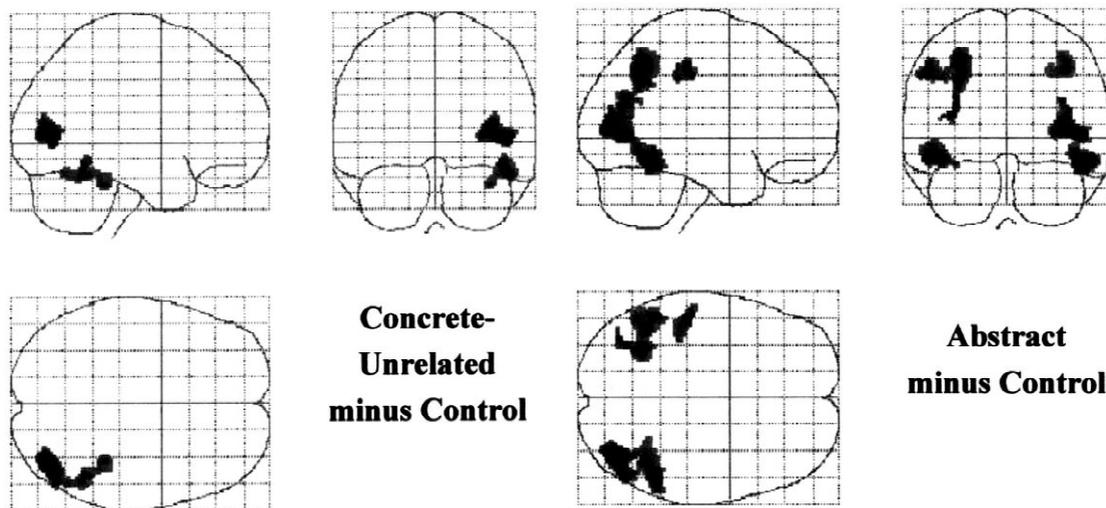


Fig. 6. Statistical parametric mapping of significant age-related differences in activation during encoding of concrete-unrelated (left) and abstract (right) pictures. The clusters are those areas in which younger subjects had a greater signal increase than older adults. For locations and peak values see Table 4.

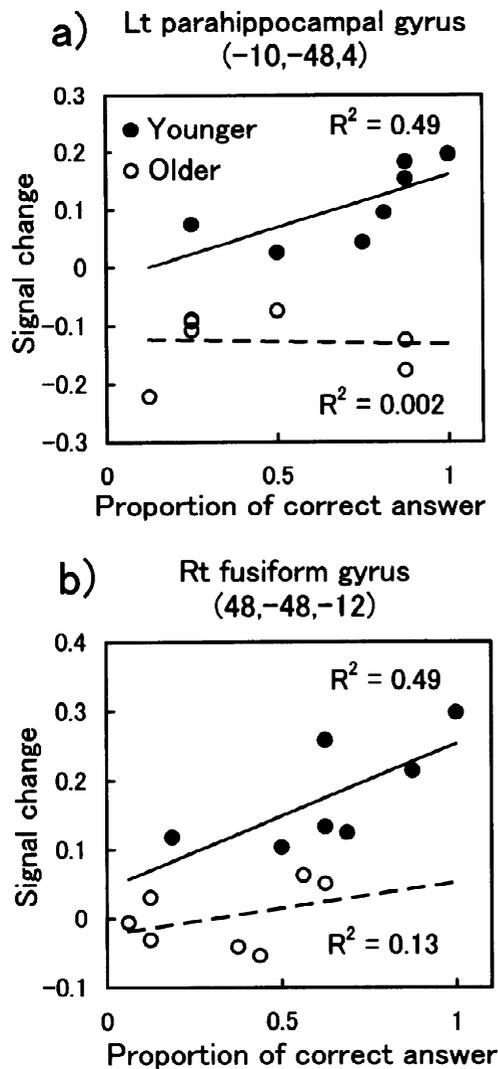


Fig. 7. The results of correlation analysis are shown. An  $x$ -axis represents the proportion of correct answer in the post-scan recognition test and a  $y$ -axis represents the amplitude of signal change between the task condition and the control condition. (a) The younger subjects (filled circles and filled line) had a positive correlation between memory performance and signal change in the left parahippocampal gyrus under the CU condition, but the old subjects (open circles and dotted line) did not. (b) The younger subjects (filled circles and filled line) had a positive correlation between memory performance and signal change in the right fusiform gyrus, but the old subjects (open circles and dotted line) did not.

pictures. Our results replicate those of the study by Kelly et al. [24] that reported the bilateral PFC activation during the encoding of concrete pictures. However, there was no significant activation in the frontal lobe under the CR condition, a finding that is probably due to the less demanding nature of the task as revealed by the near ceiling performance of the subjects. A subtraction between conditions revealed that the left dorsal PFC had greater signal intensity under the CU and AB conditions as compared to the CR condition. A possible interpretation of the recruitment of the left dorsal PFC is that greater cognitive effort was required while subjects are making a

meaningful association between two unrelated-concrete pictures, and to the same extent during the learning of pairs of abstract pictures. This hypothesis is supported by studies showing greater activity in the left PFC during deep semantic analyses of words [4,23] and during working memory tasks [40]. Another prefrontal activation under the CU condition is located in the ventral part of the left inferior frontal gyrus. Ricci et al. [36] have reported that the left ventral PFC is activated when subjects are making a semantic association between real objects. Wagner et al. [45] have suggested that the left inferior PFC may act as a semantic executive system mediating long-term semantic knowledge. The CU condition in the present study involving processes of semantic and integrative association between unrelated pictures likely recruited both of dorsal and ventral regions in the left frontal lobe.

Activity in the right dorsal PFC was enhanced under the CU and AB conditions, presumably indicating an increase in cognitive demands. Only a few neuroimaging studies have used non-verbal materials in episodic encoding tasks [21,25,37,46], however, these studies have consistently found that activity in the right frontal lobe is critical for the encoding of abstract materials. Thus, the right dorsal PFC activation in the present study most likely reflects the cognitive processing of non-verbal features of stimuli such as physical attributes or spatial information. Conjoint activity in the bilateral PFC may help in the performance of verbal and non-verbal mnemonic operations during picture encoding.

Activation in the SPL was left-lateralized under the CU condition and was bilateral under the AB condition. It is likely that greater visuospatial attention was required under the abstract condition than under the concrete conditions. Several neuroimaging studies have determined that the posterior parietal cortex is specifically involved in the encoding of abstract pictures [25] or checkerboard patterns [21]. In an fMRI study by Kraut et al. [27], the bilateral superior parietal lobule was activated during judgments of object shape. The region in the intra-parietal sulcus has been implicated in visuospatial attention and eye movement [9,10,32]. A finding that the subtraction of the CR condition from the AB condition showed significant activity in the right intraparietal sulcus is consistent with these previous studies.

#### 4.2. Activation in older adults and age-related changes

During the encoding of pictures, the older adults showed less activation of those areas responsible for intentional learning of stimuli than did the younger adults. Most importantly, a direct comparison between groups demonstrated age differences under the CU and AB conditions. There was no evidence for functional compensation in the older adults because no region had a greater signal increase in the older adults compared to the younger adults. However, the older adults activated the left dorsal PFC, the

medial frontal, and the lateral premotor regions under the CU and AB conditions.

The subtraction of the older from the younger adults under the CU condition yielded significant differences in the right occipito-temporal areas (Fig. 6, left), extending to the anterior part of the fusiform gyrus. Grady et al. [19] reported that activity in the right inferior temporal lobe during picture encoding was significantly reduced in the old subjects. The present result showing reduced activation in the ventral part of the temporal lobe indicates insufficient encoding processes in the older adults. Several authors [22,35] have suggested that non-verbal picture information such as physical or spatial attributes are processed in the right hemisphere, while verbal information such as the name or other semantic information is processed in the left hemisphere. According to these studies, our results suggest that older adults' encoding processes for non-verbal features of objects are impaired.

During the encoding of abstract pictures, large areas in the bilateral temporo-parietal and occipital lobe showed significant between-group differences (Fig. 6, right). This is a reflection of greater signal increases in the younger adults compared to minimal or no changes in the older adults. As reported in the results for the young adults, these regions appeared to play a critical role in processing visuo-spatial information from pictures such as the shape and contour of stimuli. In a behavioural study by Smith et al. [39], older subjects had reduced memory performance during abstract picture encoding compared to younger subjects. Another study has shown that visuo-spatial performance declines with aging more rapidly than verbal performance [26]. We predicted that older adults would have reduced activity in areas associated with the learning of abstract pictures. Accordingly, an impaired ability to memorize these stimuli was partly attributable to reduced activation in the bilateral temporo-parieto-occipital areas in older adults. Other neuroimaging studies have found age differences in the left inferior temporal lobe during the encoding of faces [16], and in the left temporal, occipital, and right fusiform regions during the encoding of word pairs [6]. The results of previous studies showing a lack of activation in the posterior part of the brain in older adults are consistent with the results of the present study.

What is the neurophysiological basis of age differences in activation observed in the present study? First, several studies have found that the glucose metabolism [30] or blood flow [47] in the parietal lobe is negatively correlated with age. Horwitz et al. [20] have reported that cortical pathways between the parietal and frontal lobes are vulnerable to aging. Moreover, metabolic asymmetry in the parietal lobe is significantly correlated with the relative discrepancy between verbal and visual memory performance in healthy elderly subjects [1]. These metabolic changes in older subjects are confirmed by neuropathological findings [15]. Second, several authors reported that the relationship between brain activation and BOLD signal

responses may be altered in elderly subjects. Ross et al. [38] found that the amplitude of signal response in elderly subjects was significantly decreased compared to younger subject during photic stimulation. Taoka et al. [42] reported that the time lag between onset of task and rise of signal response was prolonged with increasing age. Age differences were also observed in the signal-to-noise ratio and motion artifact of the imaging data [12]. These findings may represent reduced neuronal activation, reduced vascular response to normal activation, structural change, or an alteration in the coupling of blood oxygenation changes in response to focal activation in the elderly subjects.

Separate group analysis showed that the older adults failed to activate the left ventral and the right dorsal PFC under the CU condition even at lower threshold ( $P=0.01$ ). However, between-group analysis did not show age difference in these cortical regions, probably due to the small number of subjects. Cabeza et al. [5,6] have found that older subjects have reduced activity in the left ventral PFC during the encoding of word pairs as compared to younger subjects. Similarly, younger subjects showed a significant activation of the ventral PFC during the working memory task, but older subjects did not [18]. The lack of activation in the right dorsal PFC for the older adults may relate to an impaired processing of non-verbal information because this region is specifically involved in the encoding and working memory tasks for non-verbal materials [21,25,37,46].

Another question concerns the significant activation in the left dorsal PFC that was found in both the younger and older adults under the CU and AB conditions. In addition, there was no age difference in activation of the inferior temporal lobe under the CR condition. These results indicate that the older adults in the present study were able to enhance neuronal activity in these cortical regions of the frontal and temporal areas at a significant level although they performed the tasks significantly worse than did the younger adults. Several accounts may be possible for this discrepancy. First, cortical regions activated by the older adults as significantly as the younger adults are essentially involved in picture encoding as indicated by other neuroimaging studies [17,21,27]. For example, Grady et al. [19] found significant activation in the left prefrontal cortex during picture encoding both in young and old subjects. Such activation may help to explain the preserved picture memory in older adults as compared to word memory [11]. Second, memory performance reflects cognitive processes both during encoding and during retrieval; in contrast, neuroimaging data in the present study reflect only neural process during encoding. Age-related differences during retrieval reported by neuroimaging studies [5,7,29] suggest that lower memory performance in the older adults is partly attributed to reduced activation during retrieval. Third, lack of activation in the parieto-occipital lobe disconnected neural network between frontal lobe and posterior part of the brain under AB condition, and reduced

memory performance in the older adults in spite of significant activation in the left prefrontal cortex.

The results of correlation analysis revealed significant age difference in regression slope between memory performance and brain activity. A particularly notable finding was that the posterior part of the parahippocampal gyrus and the bilateral inferior temporal lobe had group-specific changes in the contribution of memory performance to brain activity. The result implies that the younger subjects with higher performance activated these regions more greatly than those with poorer performance. Both parahippocampal gyrus and fusiform gyrus are significantly involved in picture encoding [17,24,27]. The magnitude of activation in the parahippocampal gyrus predicted later memory performance for pictures [3]. The findings suggest that the pictorial information was effectively processed in these regions of the younger adults, but not in the older adults.

There are some arguments regarding association between low educational background and risk of dementia and Alzheimer's disease [8,28]. Letenneur et al. [28] found that the incidence of dementia was higher in the group of no education or primary school level. Therefore, it is possible to suggest that a significant difference in educational years between the younger and older adults affects the results of brain activation. However, it is unlikely that this is the case because the educational level of the older adults examined in the present study (university level: 6 subjects, high school level: 1 subject) was higher than that in previous studies.

The limitation of the present study was that the small number of subjects in each group may have affected the results. That between-group comparison did not reveal significant age differences in brain regions in which the young group had activation and the old group did not may indicate weak statistical power. However, the present study adopted the random effect model [14] to make the inference at the population level, and could provide reliable evidence regarding age difference in the neural substrates of picture memory. In conclusion, the results for the younger adults suggest that neural networks between the frontal lobe and posterior cortical areas mediate the encoding of pictures. The left dorsal PFC was specifically engaged while subjects were making associations between concrete-unrelated pictures and between abstract pictures. In addition, the area in the right intraparietal sulcus was significantly more active during the learning of abstract pictures. The older adults failed to activate several regions of the brain during picture encoding. A direct comparison between groups revealed that activation in the right occipito-temporal areas is greater in younger than in older adults during the encoding of concrete-unrelated pictures. Significant differences in the bilateral occipito-temporo-parietal lobes during abstract picture encoding likely underlie the difficulty in encoding abstract pictures for the older adults. These results imply that age-related declines

in picture memory are mainly related to neurophysiological changes in the temporo-parietal areas.

## Acknowledgements

This study was supported by grants for the 'Research for the Future' Program from the Japan Society for the Promotion of Science (JSPS-RFTF97L00203). We thank Takehiko Nishimoto for providing abstract pictures.

## References

- [1] A. Berardi, J.V. Haxby, C.L. Grady, S.I. Rapoport, Asymmetries of brain glucose metabolism and memory in the healthy elderly, *Dev. Neuropsychol.* 7 (1991) 87–97.
- [2] G.H. Bower, M.B. Karlin, A. Dueck, Comprehension and memory for pictures, *Memory Cogn.* 3 (1975) 216–220.
- [3] J.B. Brewer, Z. Zhao, J.E. Desmond, G.H. Glover, J.D. Gabrieli, Making memories: brain activity that predicts how well visual experience will be remembered, *Science* 281 (1998) 1185–1187.
- [4] R.L. Buckner, W.M. Kelly, S.E. Petersen, Frontal cortex contributes to human memory formation, *Nature Neurosci.* 2 (1999) 311–314.
- [5] R. Cabeza, C.L. Grady, L. Nyberg, A.R. McIntosh, E. Tulving, S. Kapur, J.M. Jennings, S. Houle, F.I.M. Craik, Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study, *J. Neurosci.* 17 (1997) 391–400.
- [6] R. Cabeza, A.R. McIntosh, E. Tulving, L. Nyberg, C.L. Grady, Age-related differences in effective neural connectivity during encoding and recall, *NeuroReport* 8 (1997) 3479–3483.
- [7] R. Cabeza, N.D. Anderson, S. Houle, J.A. Mangels, L. Nyberg, Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study, *J. Cogn. Neurosci.* 12 (2000) 197–206.
- [8] J.L. Cobb, P.A. Wolf, R. Au, R. White, R.B. D'Agostino, The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study, *Neurology* 45 (1995) 1707–1712.
- [9] M. Corbetta, E. Akbudak, T.E. Conturo, A.Z. Snyder, J.M. Ollinger, H.A. Drury, M.R. Linenweber, S.E. Petersen, M.E. Raichle, D.C. Van Essen, G.L. Shulman, A common network of functional areas for attention and eye movements, *Neuron* 21 (1998) 761–773.
- [10] J.T. Coull, A.C. Nobre, Where and when to pay attention: the neural system for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI, *J. Neurosci.* 18 (1998) 7426–7435.
- [11] F.I.M. Craik, J.M. Jennings, Human memory, in: F.I.M. Craik, T.A. Salthouse (Eds.), *Handbook of Aging and Cognition*, Erlbaum, Hillsdale, 1992, pp. 51–110.
- [12] M. D'Esposito, E. Zarahn, G.K. Aguirre, B. Rypma, The effect of normal aging on the coupling of neural activity to the bold hemodynamic response, *Neuroimage* 10 (1999) 6–14.
- [13] K.J. Friston, A.P. Holmes, K.J. Worsley, J.P. Poline, C.D. Frith, R.S.J. Frackowiak, Statistical parametric maps in functional imaging: a general linear approach, *Human Brain Mapp.* 2 (1995) 189–210.
- [14] K.J. Friston, A.P. Holmes, K.J. Worsley, How many subjects constitute a study?, *Neuroimage* 10 (1999) 1–5.
- [15] P. Giannakopoulos, P.R. Hof, J.P. Michel, J. Guimon, C. Bouras, Cerebral cortex pathology in aging and Alzheimer's disease: a quantitative survey of large hospital-based geriatric and psychiatric cohorts, *Brain Res. Rev.* 25 (1997) 217–245.
- [16] C.L. Grady, A.R. McIntosh, B. Horwitz, J.M. Maisog, L.G. Ungerleider, M.J. Mentis, P. Pietrini, M.B. Schapiro, J.V. Haxby,

- Age-related reductions in human recognition memory due to impaired encoding, *Science* 269 (1995) 218–221.
- [17] C.L. Grady, A.R. McIntosh, N. Rajah, F.I.M. Craik, Neural correlates of the episodic memory encoding of pictures and words, *Proc. Natl. Acad. Sci. USA* 95 (1998) 2703–2708.
- [18] C.L. Grady, A.R. McIntosh, F. Bookstein, B. Horwitz, S.I. Rapoport, J.V. Haxby, Age-related changes in regional cerebral blood flow during working memory for faces, *Neuroimage* 8 (1998) 409–425.
- [19] C.L. Grady, A.R. McIntosh, M. Natasha Rajah, S. Beig, F.I.M. Craik, The effects of age on the neural correlates of episodic encoding, *Cereb. Cortex* 9 (1999) 805–814.
- [20] B. Horwitz, R. Duara, S.I. Rapoport, Age differences in intercorrelations between regional cerebral metabolic rates for glucose, *Ann. Neurol.* 19 (1986) 60–67.
- [21] T. Iidaka, N. Sadato, H. Yamada, Y. Yonekura, Functional asymmetry of human prefrontal cortex in verbal and non-verbal episodic memory as revealed by fMRI, *Cogn. Brain Res.* 9 (2000) 73–83.
- [22] R.F. Kaplan, M.E. Meadows, M. Verfaellie, E. Kwan, B.L. Ehrenberg, E.B. Bromfield, Lateralization of memory for the visual attributes of objects: evidence from the posterior cerebral artery amobarbital test, *Neurology* 44 (1994) 1069–1073.
- [23] S. Kapur, F.I.M. Craik, E. Tulving, A.A. Wilson, S. Houle, G. Brown, Neuroanatomical correlates of encoding in episodic memory: levels of processing effect, *Proc. Natl. Acad. Sci. USA* 91 (1994) 2008–2011.
- [24] W.M. Kelley, F.M. Miezin, K.B. McDermott, R.L. Buckner, M.E. Raichle, N.J. Cohen, J.M. Ollinger, E. Akbudak, T.E. Conturo, A.Z. Snyder, S.E. Petersen, Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding, *Neuron* 20 (1998) 927–936.
- [25] T. Klingberg, P.E. Roland, Right prefrontal activation during encoding, but not during retrieval, in a non-verbal paired-associates task, *Cereb. Cortex* 8 (1998) 73–79.
- [26] E. Koss, J.V. Haxby, C. DeCarli, M.B. Schapiro, R.P. Friedland, S.I. Rapoport, Patterns of performance preservation and loss in healthy aging, *Dev. Neuropsychol.* 7 (1991) 99–113.
- [27] M. Kraut, J. Hart, B.J. Soher, B. Gordon, Object shape processing in the visual system evaluated using functional MRI, *Neurology* 48 (1997) 1416–1420.
- [28] L. Letenneur, V. Gilleron, D. Commenges, C. Helmer, J.M. Orgogozo, J.F. Dartigues, Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project, *J. Neurol. Neurosurg. Psychiatry* 66 (1999) 177–183.
- [29] D.J. Madden, T.G. Turkington, J.M. Provenzale, L.L. Denny, T.C. Hawk, L.R. Gottlob, R.E. Coleman, Adult age differences in the functional neuroanatomy of verbal recognition memory, *Human Brain Mapp.* 7 (1999) 115–135.
- [30] D.G. Murphy, C. DeCarli, A.R. McIntosh, E. Daly, M.J. Mentis, P. Pietrini, J. Szczepanik, M.B. Schapiro, C.L. Grady, B. Horwitz, S.I. Rapoport, Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging, *Arch. Gen. Psychiatry* 53 (1996) 585–594.
- [31] T. Nishimoto, M. Takahashi, A set of nonsensical pictures (doodles) for use in experiments of memory and cognition, *Waseda Psychol. Rep.* 29 (1996) 63–90.
- [32] A.C. Nobre, G.N. Sebestyen, D.R. Gitelman, M.M. Mesulam, R.S. Frackowiak, C.D. Frith, Functional localization of the system for visuospatial attention using positron emission tomography, *Brain* 120 (1997) 515–533.
- [33] D.C. Park, A.D. Smith, R.W. Morrell, J.T. Puglisi, W.N. Dudley, Effects of contextual integration on recall of pictures by older adults, *J. Gerontol.* 45 (1990) 52–57.
- [34] A. Pavio, K. Csapo, Picture superiority in free recall: imagery or dual-coding?, *Cogn. Psychol.* 5 (1973) 176–206.
- [35] K. Perrine, J. Gershengorn, E.R. Brown, I.S. Choi, D.J. Luciano, O. Devinsky, Material-specific memory in the intracarotid amobarbital procedure, *Neurology* 43 (1993) 706–711.
- [36] P.T. Ricci, B.J. Zelkowitz, R.D. Nebes, C.C. Meltzer, M.A. Mintun, J.T. Becker, Functional neuroanatomy of semantic memory: recognition of semantic associations, *Neuroimage* 9 (1999) 88–96.
- [37] P.E. Roland, B. Gulyas, Visual memory, visual imagery, and visual recognition of large field patterns by the human brain: functional anatomy by positron emission tomography, *Cereb. Cortex* 5 (1995) 79–93.
- [38] M.H. Ross, D.A. Yurgelun-Todd, P.F. Renshaw, L.C. Maas, J.H. Mendelson, N.K. Mello, B.M. Cohen, J.M. Levin, Age-related reduction in functional MRI response to photic stimulation, *Neurology* 48 (1997) 173–176.
- [39] A.D. Smith, D.C. Park, K. Cherry, K. Berkovsky, Age differences in memory for concrete and abstract pictures, *J. Gerontol.* 45 (1990) 205–209.
- [40] E.E. Smith, J. Jonides, Storage and executive processes in the frontal lobes, *Science* 283 (1999) 1657–1661.
- [41] J. Snodgrass, M.J. Vanderwart, A standard set of 260 pictures, *Exp. Psychol. Human Learn. Memory* 6 (1980) 174–215.
- [42] T. Taoka, S. Iwasaki, H. Uchida, A. Fukusumi, H. Nakagawa, K. Kichikawa, K. Takayama, T. Yoshioka, M. Takewa, H. Ohishi, Age correlation of the time lag in signal change on EPI-fMRI, *J. Comput. Assist. Tomogr.* 22 (1998) 514–547.
- [43] J. Talairach, P. Tournoux, *Co-planar Stereotaxic Atlas of the Human Brain*, Thieme, Stuttgart, 1988.
- [44] L.G. Ungerleider, Functional brain imaging studies of cortical mechanisms for memory, *Science* 270 (1995) 769–775.
- [45] A.D. Wagner, J.E. Desmond, J.B. Demb, G.H. Glover, J.D.E. Gabrieli, Semantic repetition priming for verbal and pictorial knowledge: a functional MRI study of left inferior prefrontal cortex, *J. Cogn. Neurosci.* 9 (1997) 714–726.
- [46] A.D. Wagner, R.A. Poldrack, L.L. Eldridge, J.E. Desmond, G.H. Glover, J.D.E. Gabrieli, Material-specific lateralization of prefrontal activation during episodic encoding and retrieval, *NeuroReport* 9 (1998) 3711–3717.
- [47] G. Waldemar, S.G. Hasselbalch, A.R. Andersen, F. Delecluse, P. Petersen, A. Johnsen, O.B. Paulson, <sup>99m</sup>Tc-d,l-HMPAO and SPECT of the brain in normal aging, *J. Cereb. Blood Flow Metab.* 11 (1991) 508–521.