Table 1 *(continued)*

VNTR in 3'UTR	*N*	*Allele (numbers of repeat)*								*P*
		6 (%)	*7 (%)*	*8 (%)*	*9 (%)*	*10 (%)*	*11 (%)*	*13 (%)*	*14 (%)*	
Control	160	0.0	1	0.0	6.3	90.6	1.9	0.0	0.0	
Patients	124	0.8	2.0	0.4	4.8	89.9	0.8	0.4	0.8	0.15
Duration of psychosis										
Transient	66	0.0	1.5	0.0	2.3	93.9	0.0	0.8	1.5	
Prolonged	47	1.1	3.2	1.1	8.5	84.0	2.1	0.0	0.0	0.021
Spontaneous relapse										
Positive	41	1.2	1.2	1.2	6.1	89.0	0.0	1.2	0.0	
Negative	71	0.7	2.8	0.0	4.2	89.4	1.4	0.0	1.4	0.82
Multisubstance abuse										
No	32	0.0	4.7	0.0	0.0	92.2	1.6	1.6	0.0	
Yes	89	1.1	1.7	0.6	5.1	89.9	0.6	0.0	1.1	0.31

3'UTR region of exon 15 of the *hDAT1* gene are shown in Table 1. Distributions of the alleles of these four polymorphisms of the *hDAT1* gene were within the values expected from Hardy–Weinberg equilibrium in both groups. The heterozygosity of these polymorphisms in the Japanese population seems to be different from that in Caucasians.[11–13] In particular, the frequency of a 10-repeat allele of the VNTR, a dominant allele, was 90.6% in the controls of the present study, and this value was similar to that of previous Japanese studies,[8,14] but it was much higher than in Caucasian populations, which was around 70%.[12,13] In contrast, the frequency of the 9-repeat allele in Japanese is lower than in Caucasians. These data indicate that distributions of *hDAT1* gene polymorphisms differ among different ethnicities.

The genotypic and allelic distribution of the four polymorphisms in the *hDAT1* gene examined did not differ significantly between controls and all patients with METH dependence/psychosis. The three SNPs did not differ significantly between any clinically defined subgroup of METH psychosis. The two SNPs in exons 2 and 9 are nonsynonymous, and the other is located in the 3'UTR region. It is unlikely that these SNPs of the *hDAT1* gene affect the function of the gene. There is possibility that the results were false negative because of insufficient statistical power to detect gene with small effects. The power analysis showed that the present sample size had a power of 0.81 to detect a significant allelic association between controls and patients, but it remarkably declined to 0.44 in comparison between subgroups of METH psychosis. Reanalyses should be needed after recruit of additional cases.

The allelic distribution of the VNTR polymorphism in 3'UTR was significantly different between subgroups of the transient and prolonged psychosis types ($P = 0.021$). Patients with prolonged METH psychosis showed less frequency of multiple-substance abuse than those with transient type. It is unlikely that prolonged psychosis may result from abuse of other drugs except METH. Several lines of evidence indicate that VNTR in 3'UTR of the *hDAT1* gene affects transcription and translation of the dopamine transporter. An *in vivo* study of human subjects using ^{123}I-beta-CIT and single photon emission computed tomography showed that individuals with the 9-repeat/10-repeat genotype had a 22% reduction of DAT protein in the putamen compared with 10-repeat homozygous individuals;[15] however, this result was not confirmed by a subsequent study.[16] In *in vitro* studies using luciferase assay and COS-7 cells, Fuke *et al*[17] showed that 7- and 9-repeat alleles have lower transcription activities compared to 10- and 11-repeat alleles; however, this was not confirmed by subsequent studies either.[18] Finally, Mill *et al*[19] measured mRNA levels of DAT in brains and lymphocytes directly and demonstrated clearly that 10-repeat/10-repeat, 9-repeat/10-repeat, and 9-repeat/9-repeat genotypes had linearly decreased expression of DAT mRNA in that order. These findings indicate that genotypes with 9- or fewer repeat alleles of the VNTR have lower transcription activity of the *hDAT1* gene than those with 10- or more repeat alleles at least in Caucasian population. Although *in vivo* and *in vitro* data using human subjects or tissues of Japanese population are not available yet, it is possible that relationship between allelic variation and gene expression is similar in different ethnic populations. Therefore, alleles were divided into two groups, 9- or fewer and 10- or more repeat alleles (Table 2). Using this dichotomy, the genotypic and allelic distribution of the *hDAT1* gene significantly differed between transient-type METH psychosis and prolonged-type METH psychosis (genotype: $G = 5.66$, $P = 0.017$; allele: $G = 7.34$, $P = 0.0054$). Allelic distribution was still significant after Bonferroni's correction to avoid type I errors in multiple comparison. The odds ratio of an individual with a 9- or fewer repeat allele for prolonged type METH psychosis was 4.24 (95% CI = 2.46–7.31).

The present study demonstrated that VNTR in 3'UTR of the *hDAT1* gene was not associated with METH dependence, but it was significantly associated with worse prognosis for

Table 2 Genotypic and allelic distributions of VNTR polymorphism in 3'UTR of *hDTA1* gene polymorphisms of METH dependence/psychosis

		Genotype				Allele		
VNTR in 3'UTR	*N*	*10R/10R (%)*	*10R/9R (%)*	*9R/9R (%)*	*P*	*10R (%)*	*9R (%)*	*P*
Control	160	86.3	12.5	1.3		92.5	7.5	
Patients	124	84.7	14.5	0.8	0.63	91.9	8.1	0.80
Duration of psychosis								
Transient	66	92.4	7.6	0.0		96.2	3.8	
Prolonged	47	74.5	23.4	2.1	0.017	86.2	13.8	0.0054
Spontaneous relapse								
Positive	41	80.5	19.5	0.0		90.2	9.8	
Negative	71	85.9	12.7	1.4	0.36	92.3	7.7	0.61
Multisubstance abuse								
No	32	93.8	3.1	3.1		95.3	4.7	
Yes	89	83.1	16.9	0.0	0.06	91.6	8.4	0.31

METH psychosis. Similar findings were reported in cocaine abusers by Gelernter *et al*,[20] who found that VNTR of the *hDAT1* gene was not associated with cocaine dependence, but was associated with cocaine-induced paranoia, especially in Caucasian patients. The frequency of the 9-repeat allele was higher in patients with cocaine-induced paranoia than without it. Cocaine and METH belong to the psychostimulant agent category, and exert similar effects in the brain as indirect dopamine agonists, and their abuse can induce strong dependence and psychotic syndrome as well. A 9- or fewer repeat allele of VNTR of the *hDAT1* gene, which may produce decreased transcription of the *hDAT1* gene, could be a risk factor for development of psychostimulant-induced psychosis and its worse prognosis.

Several studies [21–23] revealed by positron emission tomography that dopamine transporters in the caudate/putamen of METH abusers were significantly decreased. Some patients showed a reduction of dopamine transporters lasting for several months[21] or several years[22] after detoxification. Sekine *et al*[22] showed a reduction of dopamine transporters not only in the caudate/putamen, but also in nucleus accumbens and prefrontal cortex of METH abusers. In addition, the rate of the reduction of dopamine transporters was significantly correlated with the duration of METH consumption and the severity of METH psychosis. These findings may suggest that every METH consumption reduces dopamine transporters one step, which may persist, accumulate, and result in a substantial reduction of dopamine transporters and, finally, development of severe psychotic symptoms. Such a lasting decrease in dopamine transporter density of METH abusers may result from potential METH-induced dopamine neurotoxicity. It is well documented in experimental animals that METH produces nerve terminal degeneration of dopamine and serotonin by multiple mechanisms.[24] As one of major mechanisms, an increased dopamine release by METH and subsequent auto-oxidation of dopamine to highly reactive free radicals should be involved. Elevated dopamine concentration in synaptic clefts is removed rapidly by reuptake through dopamine transporters. Decreased dopamine transporter density may delay dopamine clearance and enhance neurotoxicity. Based on the present findings, it is postulated that individuals with a genetically reduced density of dopamine transporters because of the presence of a 9- or fewer repeat allele of the *hDAT1* gene are more susceptible to neurotoxicity of METH and prolonged METH psychosis if they abuse METH.

SUBJECTS AND METHODS

The subjects were 124 unrelated patients with METH dependence and psychotic disorder (94 males and 21 females, aged 35.8±11.3 years) meeting the ICD-10-DCR criteria (F15.2 and F15.5) who were outpatients or inpatients of psychiatric hospitals of the Japanese Genetics Initiative for Drug Abuse (JGIDA), and 160 age-, gender-, and geographical origin-matched normal controls (125 males and 35 females, aged 36.0±10.2 years). The control group consisted mostly of medical staff members who had no past individual or family history of drug dependence or psychotic disorders. Diagnoses were made by two trained psychiatrists by interview and all available information, including hospital records. Patients were excluded if they had a clinical diagnosis of schizophrenia, any other psychotic disorder, or an organic mental syndrome. All subjects were Japanese, born and living in selected areas of Japan including northern Kyushu, Setouchi, Chube, Tokai, and Kanto. This study was performed after obtaining approval from the ethics committees of each institute of JGIDA, and all subjects provided written informed consent for the use of their DNA samples in this research.

The patients were divided into subgroups by several characteristic clinical features. The patients were divided by multiple-substance abuse status; 36 patients had abused only METH in their lifetime, and 89 patients had abused

drugs other than METH in the past or present. After METH, organic solvents were the most frequently abused drugs, followed by marijuana. Cocaine and heroine abuse were rarely seen in the present study. The course of METH psychosis varied among patients, and some patients showed continuous psychotic symptoms even after METH discontinuance, as previously reported.[25,26] Therefore, patients were divided into two categories of psychosis, the transient type and the prolonged type, based on the duration of the psychotic state after METH discontinuance. Patients with the transient type showed improvement of psychotic symptoms within 1 month after the discontinuance of METH consumption and beginning of treatment with neuroleptics, and those with the prolonged type had psychosis that continued for more than 1 month even after the discontinuance of METH consumption and beginning of neuroleptic treatment. In this study, 66 patients had the transient type and 47 had the prolonged type of METH psychosis. The subgroup of prolonged type of METH psychosis may include some patients suffering from protracted endogenous psychosis like schizophrenia with coincidental onset with transient METH psychosis. It seems difficult to exclude completely such comorbid cases from the present study. However, patients with predominant negative or disorganized symptoms, which are observed rarely in METH psychosis patients, were excluded to keep homogeneity of subgroup.

It has been well documented that once METH psychosis has developed, patients in the remission state become liable to spontaneous relapse without reconsumption of METH.[25,26] It is postulated that a sensitization phenomenon induced by repeated consumption of METH develops in the brains of METH psychosis patients and is the neural basis for enhanced susceptibility to relapse.[7] Therefore, the patients were divided into two groups according to the presence or absence of spontaneous relapse. The patients with a history of spontaneous relapse were 41 and those without were 71.

Genomic DNA was extracted from peripheral leukocytes by the standard phenol/$CHCl_3$ method. The region containing the three SNPs was amplified by PCR using a unique primer sets[11,27] and genotyping was determined as RFLP using restriction enzymes as follows: 242C>T (exon 2), 5′-AAGAGGGAAGAAGCACAGAA-3′, 5′-GGAGCTGGTGAGCTGCGGTCC-3′, and *Cpo*I; 1342A>G (exon 9), 5′-CACAGCGTGGGCTCTGTG-3′, 5′-GGTGGAAGGAACCCAACTG-3′, and *Dde*I; 2319G>A (exon 15); 5′-CCGTGTCTTGTGTTGCTGTA-3′, 5′-ACGGGGATTCTCAGGAGGTG-3′, and *Msp*I. PCR was performed in a final volume of 15 μl with 10% dimethyl sulfoxide and 1 U of Supertaq (Sawady Co., Japan) in the reaction mixture. The amplification conditions were initiated at 95°C for 5 min, followed by 35 cycles consisting of denaturation at 95°C for 1 min, annealing at the appropriate primer-pair annealing temperature for 30 s and extension at 72°C for 1 min, with a final extension step of 10 min at 72°C. After digestion, PCR products were analyzed on 2–4.5% agarose gels. VNTR polymorphism in exon 15 was amplified with 5′-TGTGGTGTAGGGAACGGCCTGAG-3′, 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′. The forward primer was 5′-end-labeled with Texas red, and PCR products and the Texas red-labeled size standard were electrophoretically run on 6% polyacrylamide gels using an SQ5500 DNA sequencer (Hitachi Co., Japan). Each length was calculated using Fragyls 2 (Hitachi Co., Japan) computer software. All genotyping was carried out in a blinded fashion with control and patient samples randomly mixed. The presence of the Hardy–Weinberg equilibrium was tested using a χ^2 goodness-of-fit test. Statistical analysis of SNPs was performed using the log-likelihood ratio test or Fisher's exact test at a significance level of 0.05, two-tailed, and that for VNTR polymorphism was conducted using the Monte-Carlo method as implemented in CLUMP.[28]

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DUALITY OF INTEREST

■■■

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Mental Visual Synthesis is Originated in the Fronto-temporal Network of the Left Hemisphere

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Mental visual synthesis is the capacity for experiencing, constructing, or manipulating 'mental imagery'. To investigate brain networks involved in mental visual synthesis, brain activity was measured in right-handed healthy volunteers during mental imagery tasks, in which the subjects were instructed to imagine a novel object, that does not exist in the real world, by composing it from two visually presented words associated with a real object or two achromatic line drawings of a real object, using functional magnetic resonance imaging (fMRI). Both tasks activated the same areas in the inferior frontal and inferior temporal cortices of the left hemisphere. Our results indicate that the source of mental visual synthesis may be formed by activity of a brain network consisting of these areas, which are also involved in semantic operations and visual imagery.

Keywords: fMRI, human brain, inferior frontal cortex, inferior temporal cortex, visual synthesis

Introduction

Mental visual synthesis is the act or power of forming a mental image of something not perceived by the senses or present in reality. It consists of taking parts of our various conceptions and combining them to give new forms and images more selective, more striking, more delightful and more terrible, among other things, than those existing in reality. There is no doubt that our brain generates mental visual synthesis. Therefore, brain networks must be activated and a population of neurons belonging to these brain networks must be activated when a person visualizes synthesized objects in their mind's eye. Although neuroimaging techniques now have sufficient potential to detect changes in neuronal activity involved in higher cognitive or mental functions, to our knowledge no brain imaging study has been performed that directly investigated the relationship between brain activity and mental visual synthesis. Therefore, in the present study, we used functional magnetic resonance imaging (fMRI) to address the question of which brain areas are involved during mental visual synthesis that is the basis of imagination.

Mental visual imagery is one of the relevant counterparts of mental visual synthesis in the context of human cognitive functions. Mental visual synthesis is the mental capacity for experiencing, constructing, or manipulating mental imagery. Mental visual imagery is defined as the manipulation of visual information arising from memory, giving rise to the experience of seeing through the mind's eye. In contrast to mental visual synthesis, there are many investigations on mental visual imagery using functional imaging techniques (for reviews, see Mellet *et al.*, 1998; Kosslyn *et al.*, 2001). One of the major controversies in previous functional imaging studies has been whether the primary visual cortex is involved in visual mental imagery. Although many of the previous studies addressed this issue, results of these studies also indicated that not only visual areas but also several brain areas are activated in relation to visual mental imagery and that the brain activation pattern varies according to the object that is mentally visualized. A significant activation of the parieto-occipital areas (often bilaterally) was reported during visual imagery tasks using mental rotation (Mellet *et al.*, 1996), route finding (Roland and Friberg, 1985; Roland *et al.*, 1987; Ghaem *et al.*, 1997) and recall of prelearned three-dimensional scenes (Mellet *et al.*, 2000), patterns (Knauff *et al.*, 2000) and spatial locations (Kawashima *et al.*, 1995). In contrast, temporo-occipital areas were significantly activated when subjects were instructed to imagine construction of concrete objects according to verbal instructions (D'Esposito *et al.*, 1997; Mellet *et al.*, 1998) and based on paired associates (Shallice *et al.*, 1994; Fletcher *et al.*, 1995) and mentally to recall prelearned patterns (Roland and Gulyas, 1995) and letters (Kosslyn *et al.*, 1993). The findings of neuroimaging studies on mental visual imagery are consistent with those of previous neuroimaging studies of visual perception showing functional dichotomy between the dorsal and the ventral pathways according to the spatial and object form perceptions, respectively (for a review, see Ungerleider and Haxby, 1994) , which was first demonstrated in monkeys (Miskin *et al.*, 1983). These findings indicate that mental visual imagery and visual perception share common and very specific mechanisms.

In the present study, we aimed to determine brain areas specifically involved in mental visual synthesis. To do this, we compared brain activity measured by fMRI during mental visual synthesis and mental visual imagery conditions. In this study, we assumed that at least the following cognitive processes have to be involved in mental visual imagery: retrieval of knowledge of two different objects from long-term semantic memory based on external cues (words or line drawings); bringing these pieces of information into working memory; holding it on-line; and seeing those objects through the mind's eye. We also assumed that mental visual synthesis requires one more specific cognitive process in addition to the above-mentioned processes, that is to create a new object by combining and modifying these pieces of information in novel ways. Since we counterbalanced visual inputs and motor outputs between mental visual synthesis and mental visual imagery conditions in this study, a comparison of mental visual

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synthesis versus object imagery may indicate brain areas involved in the specific cognitive process for visual synthesis.

Methods

Subjects

Forty-three young right-handed healthy volunteers, of ages ranging from 18 to 31 years, participated in this study. Their handedness was assessed by the Edinburgh Handedness Inventory. Written informed consent was obtained from each subject in accordance with the guidelines approved by the Tohoku Fukushi University and the Helsinki Declaration of Human Rights, 1975. Brain activity was measured in 23 subjects using fMRI during a word task and the remaining 20 subjects performed a picture task during fMRI measurement.

Tasks

The word task consisted of two experimental conditions, that is, object imagery and synthesis conditions and a baseline condition. In the object imagery condition, two different nouns of a common object, e.g. 'apple' and 'table', were presented at the center of the screen simultaneously for 1 s, followed by a 4 s inter-trial interval. During the inter-trial interval, an eye-fixation point was presented at the center of the screen. The subjects were instructed to imagine the appearance of the real objects in turn during the inter-trial interval and were asked to press a button using the right hand when they succeed to imagine two objects. In the synthesis condition (Fig. 1*A*), a compound word, which consisted of two nouns but did not indicate a real object, e.g. 'television-rock', was presented for 1 s at the center of the screen, followed by a 4 s inter-trial interval. The subjects were instructed to imagine a novel object during the inter-trial interval and were asked to press a button when they succeed in visualizing an object. Actual verbal instruction for synthesis condition was as follows; 'we ask you to create a vivid image of an object, which does not exist in the real word, in your mind from an artificial word consisting of two nouns of familiar objects'. In the base line condition, the subjects were asked to gaze at an eye fixation point. The visual inputs, that is, the presented words, were counterbalanced between the object imagery and synthesis conditions.

The picture task also consisted of two experimental conditions, that is, object imagery and synthesis conditions and a baseline condition. In the object imagery and synthesis conditions, two different achromatic line drawings of common objects were presented for 1 s at the center of the screen, followed by a 4 s inter-trial interval. During the inter-trial interval, an eye-fixation point was presented at the center of the screen. In the object imagery condition, the subjects were asked to imagine the appearance of real object in turn during the inter-trial interval and were asked to press a button when they succeed in visualizing two objects. In the synthesis condition (Fig. 1*B*), the subjects were instructed to create a novel object in their minds by compounding the two line drawings, to imagine this object during the inter-trial interval and to press a button when they succeed in visualizing this object. Actual verbal instruction for the synthesis condition was the same as for the word task. The presented line drawings were generated from the same words used in the word task. the baseline condition was the same in the word task. The visual inputs and motor outputs were counterbalanced between the object imagery and synthesis conditions.

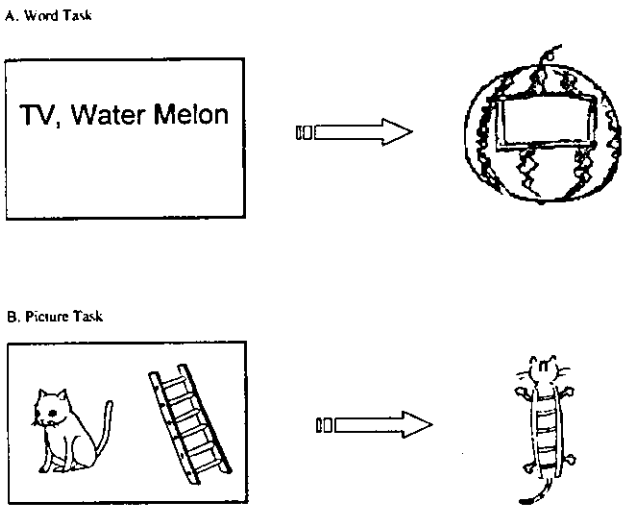

Figure 1. Diagrams of synthesis conditions. (*A*) Word task. (*B*) Picture task.

Prior to the fMRI scan, subjects were trained with both object imagery and imagination conditions. The reaction time, that is, duration between the start of the inter-trial interval and pressing the button, was measured during fMRI measurements using a personal computer. A debriefing of the subject was held immediately after each fMRI scan.

fMRI Measurements

T_1-weighted structural images were acquired for each volunteer, using a 1.5 T Siemens Vision plus scanner (T_R = 9.7 ms, echo time = 4 ms, FA = 12°, FOV = 250 mm, pixel size = 1.25 × 0.98 mm, matrix = 175 × 256; Siemens Magnetron Vision, Erlanger, Germany). To measure neural responses, gradient echo, echoplanar T_2^*-weighted images with blood oxygenation level-dependent (BOLD) contrast were acquired by GE-EPI (T_E = 60 ms, FA = 90°, matrix = 64 × 64, FOV = 256 × 256 mm, slice thickness 3 mm, gap = 2.25 mm) covering the entire brain at a T_R of 5 s. Forty-two axial slices were oriented over the whole brain. To eliminate T_1 equilibration effects, four preliminary scans were acquired and the others subsequently discarded. Thereafter, scans were acquired continuously every 5.0 s.

In the present study, a conventional block design consisting of ten alterations of a 60 s ON block and a 20 s baseline condition block was used for each task. Each of the two experimental conditions was assigned to the ON block five times in the same order for each subject (e.g. ABCABCABCABCABC) and the order of the experimental conditions was counterbalanced across the subjects. Therefore, each ON block consisted of 10 trials for each task.

Image Data Processing and Statistical Analyses

All preprocessing procedures and data analyses were performed using Statistical Parametric Mapping 99 (SPM99) software (Wellcome Department of Cognitive Neurology, London, UK) implemented on MATLAB (Mathworks Inc., Natick, MA). First, slice time adjustment was performed to correct for differences in acquisition time among 34 slices of each scan. Secondly, to correct for artifacts caused by small head movements, images from each subject were realigned to the first image and resliced using a sinc interpolation. Thirdly, a mean image created from the realigned volumes was coregistered with the structural T_1 volume and the structural volumes were spatially normalized to a standard template in the space of Talairach and Tournoux (1988) using nonlinear basis functions. Fourthly, the derived spatial transformation was applied to the realigned T_2^* volumes, which were then spatially smoothed with a three-dimensional isotropic Gaussian Kernel (12 mm full width half-maximum). This improves the signal-to-noise ratio and accommodates for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

Condition effects at each voxel were estimated according to this general linear model and regionally specific effects were compared using linear contrasts. Global changes were adjusted by a proportional scaling and low-frequency confounding effects were removed using an appropriate high-pass filter. Voxel values for each contrast yielded a statistical parametric map of the *t*-statistic (SPM *t*) and were subsequently transformed to the unit normal distribution (SPM *Z*). Then, inter-subject maps were produced by performing one-sample *t*-tests to identify voxels that survived the statistical threshold of $P < 0.05$ after correction for multiple comparisons. Finally, the resulting activation maps were constructed and superimposed onto stereotactically standardized T_1-weighted MR images.

A set of ROIs was anatomically defined for each subject on the regions that were significantly activated in the synthesis versus object

imagery comparisons. For each subject and each ROI, a mean time series, averaged across activated voxels in the region and across all runs, was calculated. We then compared the mean amplitude of fMRI signal for each condition.

Results

Task Performance

Immediately after the fMRI measurements, the subjects were asked to sketch the appearance of objects they imagined during the synthesis conditions. Examples of these sketches are shown in Figure 1.

The mean (SEM) reaction times during object imagery and synthesis conditions of the word task were 1.3 s (0.1) and 1.4 s (0.1), respectively, with no statistically significant differences (paired *t*-test). Those during object imagery and synthesis conditions of the picture task were 2.5 s (0.2) and 2.7 s (0.2), respectively, with no statistically significant differences (paired *t*-test). The reaction time in the picture task was statistically significantly longer than that in the word task (ANOVA, $P < 0.001$).

The mean (SEM) percentages of successful trials of the word task were 98.0% (2.8) and 95.0% (2.7) during object imagery and synthesis conditions with no statistically significant differences (paired *t*-test). Those during object imagery and synthesis conditions of the picture task were 93.4% (4.0) and 90.0% (5.0), respectively, with no statistically significant differences (paired *t*-test). The mean percentage of successful trials was not statistically significant between the word and picture tasks (ANOVA).

Brain Activation

Table 1 and Figure 2 summarize brain areas activated during the word task. The object imagery versus baseline comparison revealed the significant activation of the inferior frontal and inferior temporal cortices of the left hemisphere, anterior cingulate cortex, as well as bilateral cerebellum. The synthesis versus baseline comparison showed the significant activation

Table 1
Talairach coordinates and *T*-value of peak activation during the word task

Anatomical name	Talairach coordinates			*T*	Volume
	x	*y*	*z*		
Object imagery versus baseline					
Lt inferior frontal	−42	6	30	8.2	1192
Lt inferior frontal	−42	10	2	8.1	856
Lt inferior frontal	−46	24	−4	7.3	1008
Lt inferior temporal	−50	−64	−32	8.6	3848
Lt cerebellum ant lobule	−16	−88	−12	5.3	192
Rt anterior cingulate	8	14	46	6.6	392
Rt cerebellum anterior lobule	40	−42	−30	8.8	848
Rt cerebellum posterior lobule	44	−64	−26	6.4	424
Rt cerebellum posterior lobule	10	−82	−20	9.2	2904
Synthesis versus baseline					
Lt inferior frontal	−40	6	32	10.9	4192
Lt inferior frontal	−48	30	10	10.7	4320
Lt inferior temporal	−52	−60	−10	10.8	18376
Lt intraparietal	−26	−60	40	9.1	2000
Lt parahipocampal	−16	−24	−12	7.0	2112
Rt parahipocampal	22	−26	−16	5.9	200
Rt striatum	16	−4	12	7.2	2336
Anterior cingulate	8	14	48	7.2	592
Rt cerebellum anterior lobule	30	−34	−34	11.9	5016
Synthesis versus object imagery					
Lt inferior frontal	−48	6	22	8.2	1856
Lt inferior frontal	−48	30	10	10.6	4032
Lt inferior temporal	−54	−60	−8	6.9	1032
Rt striatum	16	0	14	7.6	744
Lt striatum	−12	0	12	6.0	176
Rt cerebellum posterior lobule	16	−82	−26	7.8	1680

Stereotaxic coordinates (in millimeters) identify the location of the maxima of haemodynamic responses corresponding to the atlas of Talairach and Tournoux (1988). Lt and Rt indicate left and right hemisphere, respectively. Volumes are in mm^3.

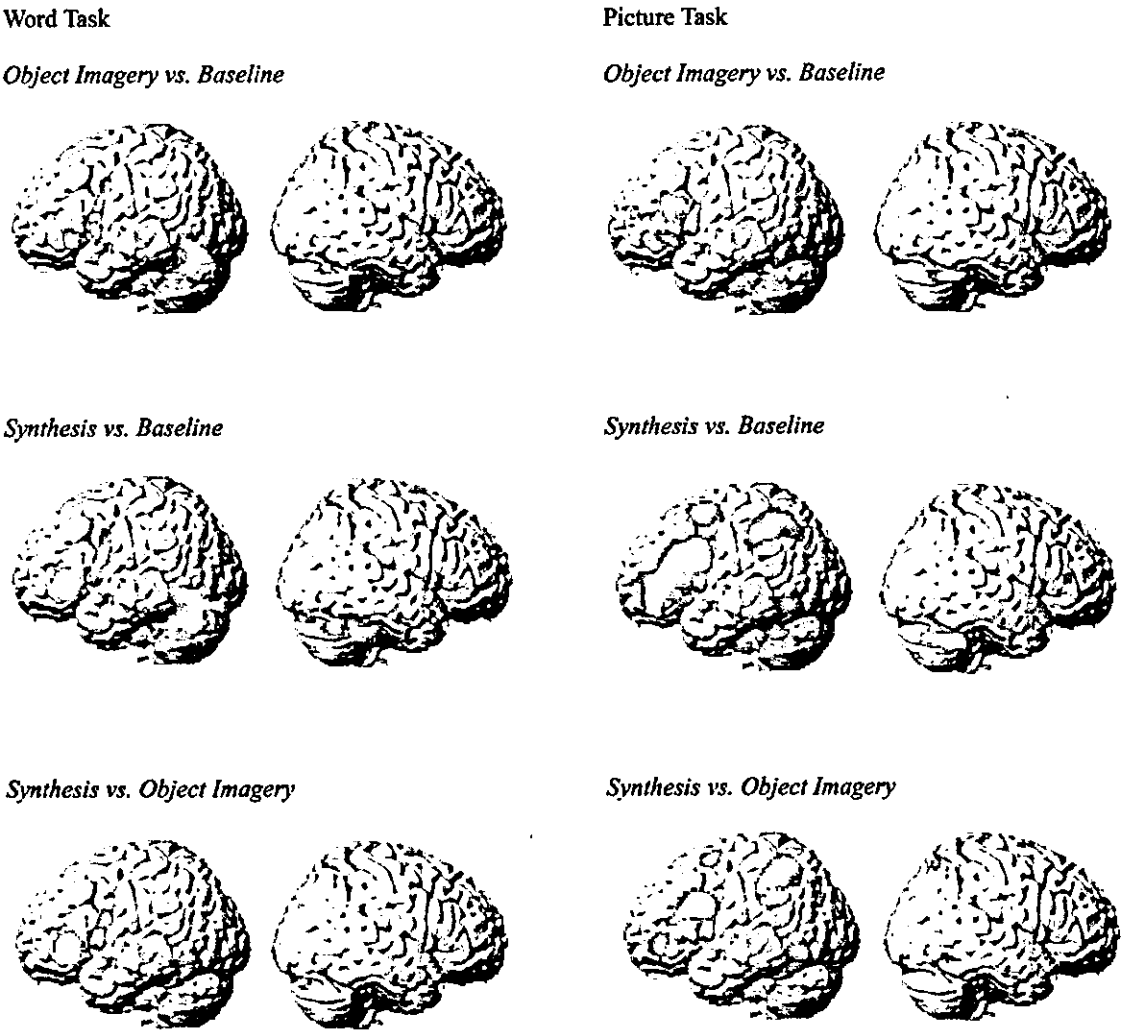

Figure 2. Surface projections of color-coded statistical parametric maps (SPMs) showing statistically significant activations. The left sides of the figures correspond to the left hemisphere. The SPMs are group maps from 23 and 20 subjects for word task and picture task, respectively. Thresholds were set at $P < 0.05$ after correction for multiple comparisons.

of the inferior frontal, inferior temporal and intraparietal cortices of the left hemisphere, anterior cingulate cortex, bilateral parahippocampal cortices, right insula and the right cerebellum. The synthesis condition more significantly activated the left inferior prefrontal cortex, left inferior temporal cortex, bilateral striatum and the right cerebellum than the object imagery condition.

Table 2 and Figure 2 summarize brain areas activated during the picture task. The object imagery versus baseline comparison showed significant activation of the left inferior frontal cortex, anterior cingulate cortex and bilateral cerebellum. Although subjects looked at the line drawing pictures during the object imagery condition, activation of the primary visual cortex did not reach a statistically significant level. The synthesis versus baseline comparison revealed the significant activation of the bilateral inferior frontal, left inferior temporal, left intraparietal, left fusiform and anterior cingulate cortices, as well as the right striatum and right cerebellum. The synthesis condition more significantly activated the left inferior frontal, bilateral inferior temporal, bilateral intraparietal and left lateral occipital cortices than the object imagery condition. A larger extent of activation was evoked by the picture task compared with the word task in each comparison.

It should be noted that the same two areas in the left inferior frontal cortex, one in the anterior region, the other in the posterior region and an area in the posterior part of the left inferior temporal cortex were significantly activated during the synthesis condition compared with the object imagery condition during both tasks (Fig. 2). The anterior and posterior regions of the inferior frontal gyrus are probably located in the orbital and opercular parts of the inferior frontal gyrus, respectively. The magnitude of activation in these areas during each condition was not statistically significant (Student's *t*-test) between the picture and word tasks (Fig. 3).

Discussion

Our results indicate that the neuronal network consisting of the inferior frontal and the inferior temporal cortices of the left

Table 2
Talairach coordinates and *T*-value of peak activation during the picture task

Anatomical name	Talairach coordinates			*T*	Volume
	x	*y*	*z*		
Object imagery versus baseline					
Lt inferior frontal	−38	24	24	10.2	4808
Lt inferior frontal	−32	52	16	8.9	392
Lt inferior frontal	−32	26	−4	8.8	2176
Anterior cingulate	−10	6	52	9.3	5656
Lt cerebellum anterior lobule	−40	−48	−24	7.9	1464
Rt cerebellum anterior lobule	38	−44	−32	15.4	3936
Synthesis vers Lt middle frontal us baseline	−22	0	60	11.2	11944*
Lt inferior frontal	−48	16	24	15.0	29552**
Lt inferior frontal	−50	30	28	15.9	29552**
Lt inferior frontal	−46	46	−4	11.4	29552**
Rt inferior frontal	48	36	12	7.1	248
Lt intraparietal	−32	−50	44	11.1	13752
Lt inferior temporal	−50	−56	−12	10.4	3776
Rt striatum	16	−2	12	7.1	168
Anterior cingulate	6	20	44	14.2	11944*
Rt cerebellum anterior lobule	36	−48	−36	10.9	7608
Synthesis versus object imagery					
Lt middle frontal	−26	6	66	10.1	1352
Lt inferior frontal	−46	10	26	11.4	7448
Lt inferior frontal	−48	48	−4	9.7	1392
Lt intraparietal	−36	−48	46	11.0	10552
Rt intraparietal	26	−66	52	7.7	320
Lt inferior temporal	−52	−62	−10	13.7	2280
RT inferior temporal	56	−60	−12	7.9	200
Lt lateral occipital	−30	−74	32	9.4	1568

Details are as in Table 1; * and ** indicate that these activation peaks were observed in one activation cluster.

hemisphere plays an important role in creating an entirely new image in one's mind.

In this study, we assumed that in order to perform the synthesis condition of each task, at least following the three cognitive processes are involved: (i) retrieval of information, that is, knowledge of two different objects, from long term semantic memory provided by external cues (words or line drawings) and bringing this information into working memory and holding it on-line; (ii) creation of a new object by combining and modifying this information in novel ways; and (iii) visualize that object through the mind's eye. We also assumed that processes (i) and (iii) are necessary to perform the object imagery condition as well. Therefore, visual inputs and motor outputs were counterbalanced between the object imagery and synthesis conditions during each task; a comparison of synthesis versus object imagery may indicate brain areas involved in the creation of entirely new objects by combining two different representations of the objects.

Hemispheric Asymmetry

We found that both object imagery and synthesis evoked the left-lateralized activation of the fronto-temporal network. The similar hemispheric asymmetry was suggested by brain imaging studies of visual imagery of familiar objects (D'Esposito *et al.*, 1997; Ishai *et al.*, 2000, 2002). On the other hand, the activation of the right inferior temporal cortex has also been reported during the mental imagery of complex objects or schematic objects (Mellet *et al.*, 1996) and letters (Kosslyn *et al.*, 1993). Mellet *et al.* (1998) reviewed previous brain imaging studies and concluded that functional lateralization during mental imagery can depend on two different characteristics of mental images to be generated: complexity, which would modulate the degree of involvement of the right hemisphere; and lexicality, which would drive the left hemisphere participation.

Farah (1986) found that left hemisphere was better at using imagery to prime perceptual recognition by a psychophysical study of normal subjects, although Kosslyn *et al.* (1985) found that in split-brain patients this left-hemisphere advantage was selective, occurring only for multipart images and that both hemispheres were equally adept at generating single-unit images of an overall shape. Kosslyn *et al.* (1995) suggested that left hemisphere more effectively generates images by arranging parts according to descriptions (using categorical spatial rela-

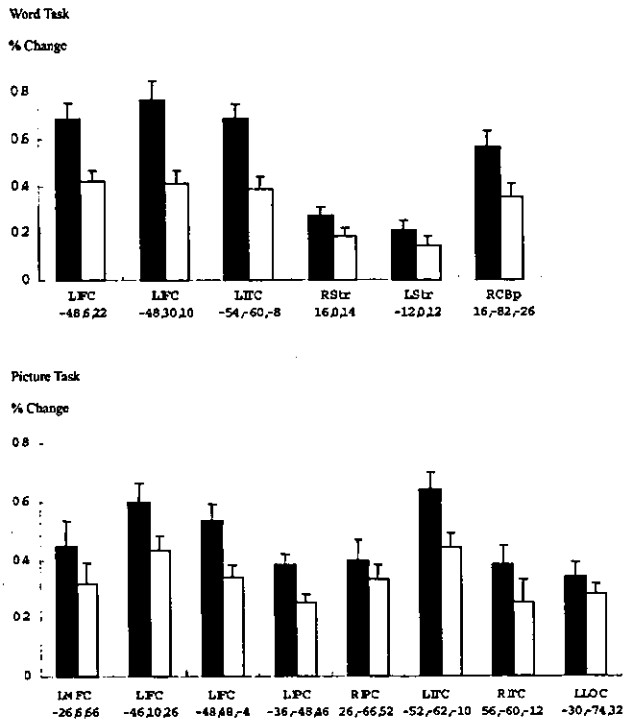

Figure 3. Mean amplitude of fMRI signal in significantly activated areas in synthesis versus object imagery comparisons. Black and white bars indicate mean amplitude during the synthesis and object imagery conditions, respectively. Error bars indicate standard error of the mean (SEM). MFC, middle frontal cortex; IFC, inferior frontal cortex; IPC, intraparietal cortex; ITC, inferior temporal cortex; Str, striatum; CBp, posterior lobule of the cerebellum; L, left hemisphere; R, right hemisphere.

tions) whereas the right hemisphere more effectively generates images by positioning parts in precise locations in space (using coordinate spatial relations) from the results of their psychophysical experiments. Although there is no doubt that both hemispheres can generate visual mental images, the specific functional role for each hemisphere in visual mental imagery still remains unclear. The variability in these findings might reflect differences in the specific combinations of processes engendered by the instructions, nature of the stimuli and subject's previous experience (Kosslyn *et al.*, 1995).

The results of the present study indicate that mental visual synthesis shares common neural substrates with object imagery, that these substrates, that is the inferior frontal and inferior temporal cortices of the left hemisphere, play roles in creating mental images from long-term memory and manipulating these in the mind's eye, that the synthesis condition differs from the object imagery condition in a quantitative rather than a qualitative way and that the left-lateralized activation may be resulted from intense lexical and categorical processing required for mental visual synthesis.

Inferior Frontal Cortex

We defined two distinct areas in the inferior frontal cortex of the left hemisphere involved in mental visual synthesis. These two areas were also activated during the object imagery condition, although they were more significantly activated during the synthesis condition.

The previous neuroimaging investigations suggested that there is no doubt the inferior frontal cortex is involved in semantic processing. One of the functional roles of the inferior frontal cortex derived from the results of previous neuroimaging studies is semantic generation. Previous positron emission tomography (PET) studies of verb generation tasks, that is, to generate semantically appropriate verbs from the presented nouns, reported activation of the left inferior frontal cortex (Petersen *et al.*, 1988; Raichle *et al.*, 1994; Tatsumi *et al.*, 1999). This area is also activated when subjects name colors (Wiggs *et al.*, 1999) or generate action words (Martin *et al.*, 1995) from visually presented line drawings of objects. Vandenberghe *et al.* (1996) also suggested that the left inferior frontal cortex is commonly activated when subjects make semantically based decisions on both presented words and pictures. Another functional role of the inferior frontal cortex determined from brain imaging studies is retrieval of semantic knowledge. Previous PET studies using picture naming paradigms indicate involvement of the left inferior frontal cortex in category-specific retrieval (Damasio *et al.*, 1996; Martin *et al.*, 1996; Grabowski *et al.*, 1997). fMRI studies of semantic category generation and semantic memory tasks also activated this area (Shaywitz *et al.*, 1995; Gabrieli *et al.*, 1998; Crosson *et al.*, 1999). In addition, some studies indicated that the inferior frontal cortex is involved in not only for retrieval but also semantic encoding (Demb *et al.*, 1995; Owen *et al.*, 1996; Nyberg *et al.*, 1996). Demb *et al.* (1995) suggested that the inferior frontal cortex is part of a semantic executive system that contributes to the on-line retireval of semantic information, similar to executive systems in a model or working memory (Baddeley, 1986; Goldman-Rakic, 1987). However, the inferior frontal cortex was not activated during the Tower of London task, which required motor planning and working memory (Baker *et al.*, 1996), or during non-verbal encoding tasks (Golby *et al.*, 2001). The results of previous studies suggest that the inferior frontal cortex is involved in semantic encoding and retrieval. The other function is selection of semantic knowledge. The prefrontal cortex has been argued to produce flexible and context-sensitive responses (Cohen and Servan-Schreiber, 1992) and to mediate the selection of action by the weighing of information active in working memory (Kimberg and Farah, 1993). From the results of an fMRI study, Thompson-Schill *et al.* (1997) found that demands on the inferior frontal cortex are high in any task that requires selection among competing sources of information in working memory to guide a response. Since semantic generation, retrieval of semantic knowledge from presented words or pictures and selection of semantic knowledge are important cognitive process for mental visual synthesis, we assumed that the results of our study are in agreement with those of previous imaging studies and that several different semantic modules in the inferior frontal cortex are responsible to mental visual synthesis.

Although, in this study, we were unable to determine functional dissociations of the anterior and posterior regions of the left inferior frontal cortex, some previous neuroimaging studies indicated interesting functional differences between the two regions. Poldrak *et al.* (1999) and Heim *et al.* (2003) suggested from the results of their fMRI studies that the anterior region subserves semantic processing and the posterior region subserves phonological processing. Bokde *et al.* (2001) obtained consistent results from functional connectivity ana-

lysis using fMRI. Fletcher and Henson (2001) summarized from the literature review that the anterior region is involved in the semantic contribution to successful encoding and the posterior region is involved in selection from various semantic attributes. At the moment, we cannot explain for the differences in functional organization of these two regions, although we can argue that the two regions may have different functional roles and that the both areas are involved in mental visual synthesis.

In summary, since inferior frontal cortex was activated during the object imagery as well as synthesis conditions and was more significantly activated during the synthesis condition, the difference in the inferior frontal activation between these two conditions may well be resulted from the difference in the semantic demands of the tasks.

Inferior Temporal Cortex

In this study, the posterior part of the inferior temporal cortex was more activated during the synthesis condition than during the imagery condition in both tasks. Activation of the same area was reported in the previous brain imaging studies during retrieval of object features (Haxby *et al.*, 1994; Kohler *et al.*, 1995; Moscovitch *et al.*, 1995; Martin *et al.*, 1996; Owen *et al.*, 1996) and encoding of object features (Owen *et al.*, 1996). This area has been considered as a target of the ventral stream (Miskin *et al.*, 1983) originating from the visual cortex, which is specialized for processing object forms (for reviews, see Goodale, 1993; Ungerleider and Haxby, 1994). Previous lesion studies of humans revealed that the posterior temporo-occipital damage impairs mental-image generation (Sergent, 1989; Tippet, 1992; Trojano and Grossi, 1994; Farah, 1995). Therefore, it is argued that the inferior temporal cortex is involved in object mental imagery and perception (Mellet *et al.*, 1998). The involvement of the left inferior temporal cortex in semantic processing was also reported in previous brain imaging studies (Tranel *et al.*, 1997; Martin *et al.*, 2000). Since one can easily build a mental image based on a verbal description (Denis and Cocude, 1992), or provide an oral description of a mental image, we may argue that strong interactions exist between language and mental imagery that permit an easy transfer from one representation mode to the other and that the interactions may take place in the inferior temporal cortex. It should be noted that a recent fMRI study by Bokde *et al.* (2001) indicated strong functional connectivity between anterior or posterior regions of the left inferior frontal cortex and the posterior part of the inferior temporal cortex during phonological processing of words. Their findings support our results, since we noted that the inferior temporal cortex was co-activated with the left inferior frontal cortex during the synthesis condition.

Notes

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