actions during the cognitive process (Laroche et al., 2000; Thierry et al., 2000; Goto and Grace, 2008).

In this study, we measured both D_1 and D_2 receptors in PFC and HPC using PET in normal healthy subjects, and aimed to elucidate how regional D_1 and D_2 receptors are differentially involved in neurocognitive performance including memory and frontal lobe functions. A body of animal studies has indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped dose–response curve, such that too little or too much D_1 receptor stimulation impairs PFC functions (Goldman-Rakic et al., 2000; Williams and Castner, 2006; Vijayraghavan et al., 2007). We hypothesized that prefrontal D_1 receptors would be more related to frontal lobe functions than prefrontal D_2 receptors, and that, specifically, an inverted U-shaped relation between prefrontal D_1 receptor binding and prefrontal functions would be observed in the normal physiological condition in healthy volunteers. In addition, we predicted that D_2 receptors in HPC would be more related to memory than D_1 receptors in HPC.

Materials and Methods

Subjects. Twenty-three healthy male volunteers [mean age 25.7 ± (SD) 4.3 years] were studied. Seven of the 23 subjects had participated in our earlier study (Takahashi et al., 2007). They did not meet the criteria for any psychiatric disorder based on unstructured psychiatric screening interviews. None of the controls were using alcohol at the time, nor did they have a history of psychiatric disorder, significant physical illness, head injury, neurological disorder, or alcohol or drug dependence. All subjects were right-handed according to the Edinburgh Handedness Inventory. All subjects underwent magnetic resonance imaging (MRI) to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all subjects, and the study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba Japan.

PET scanning. PET studies were performed on ECAT EXACT HR+ (CTI; Siemens). The system provides 63 planes and a 15.5 cm field of view. To minimize head movement, a head fixation device (Fixster) was used. A transmission scan for attenuation correction was performed using a germanium 68–gallium 68 source. Acquisitions were done in three-dimensional mode with the interplane septa retracted. For evaluation of D_1 receptors, a bolus of 213.9 ± 20.5 MBq of [^{11}C]SCH23390 with specific radioactivities (52.1 ± 28.9 GBq/μmol) was injected intravenously from the antecubital vein with a 20 ml saline flush. For evaluation of extrastriatal D_2 receptors, a bolus of 215.4 ± 24.5 MBq of [^{11}C]FLB457 with high specific radioactivities (171.0 ± 58.0 GBq/μmol) was injected in the same way. The mean injected amounts of [^{11}C]SCH23390 and [^{11}C]FLB457 were 1.18 ± 0.20 μg and 0.47 ± 0.17 μg, respectively. Dynamic scans were performed for 60 min for [^{11}C]SCH23390 and 90 min for [^{11}C]FLB 457 immediately after the injection. All emission scans were reconstructed with a Hanning filter cutoff frequency of 0.4 (full width at half maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems) (1.5 T). T1-weighted images of the brain were obtained for all subjects. The scan parameters were 1-mm-thick, three-dimensional T1 images with a transverse plane (repetition time/echo time, 19/10 milliseconds; flip angle, 30°; scan matrix, 256 × 256 pixels; field of view, 256 × 256 mm; number of excitations, 1).

Quantification of D_1 and D_2 receptors in PFC and HPC. The tissue concentrations of the radioactivities of [^{11}C]SCH23390 and [^{11}C]FLB457 were obtained from regions of interest (ROIs) defined on the PET images of summated activity for 60 and 90 min, respectively, with reference to the individual MRIs that were coregistered on summated PET images and the brain atlas. The regions were PFC, HPC and cerebellar cortex. Each ROI consisted of three axial slices. ROI of PFC occupies the middle third of the middle frontal gyrus and the rostral portion of the inferior frontal gyrus (approximately corresponding to the dorsolateral prefrontal cortex or Brodmann area 46). ROI of HPC was set at the level of the midbrain. The anterior boundary was identified at the level of the inferior horn of the lateral ventricle. The posterior boundary was identified at the level of the collateral sulcus. Although [^{11}C]FLB457 accumulates to a high degree in the striatum, striatal data were not evaluated because the duration of the [^{11}C]FLB457 PET study was not sufficient to obtain equilibrium in the striatum (Olsson et al., 1999; Suhara et al., 1999). Quantitative analysis was performed using the three-parameter simplified reference tissue model (Lammertsma and Hume, 1996). The cerebellum was used as reference region because it has been shown to be almost devoid of D_1 and D_2 receptors (Farde et al., 1987; Olsson et al., 1999; Suhara et al., 1999). The model provides an estimation of the binding potential ($BP_{ND\ (nondisplaceable)}$) (Innis et al., 2007), which is defined by the following equation: $BP_{ND} = k3/k4 = f2\ Bmax/[Kd\ [1 + \sum i\ Fi/Kdi]]$, where k3 and k4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f2 is the "free fraction" of nonspecifically bound radioligand in brain, Bmax is the receptor density, Kd is the equilibrium dissociation constant for the radioligand, and Fi and Kdi are the free concentration and the dissociation constant of competing ligands, respectively (Lammertsma and Hume, 1996).

Neuropsychological tests. A battery of cognitive tests was given by an experienced clinical neuropsychologist. The neuropsychological tests used were Rey's Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth's Complex Figure Test (ROCFT), Keio version of the Wisconsin Card Sorting Test (WCST) (Igarashi et al., 2002), Verbal Fluency Test, and Raven's Colored Progressive Matrices (RCPM). RAVLT is used to evaluate the performance of verbal memory, and ROCFT is used as a measure of nonverbal visual memory. RAVLT and ROCFT were performed in the standard manner (Lezak, 1995). In RAVLT, 15 words were presented auditorily in the same sequence in five trials, ending with a free recall of the words (immediate recall). After the five trials, an interference list was presented and recalled, and then the subjects were instructed to recall the first list of words (delayed recall). In ROCFT, after the copy trial, subjects were asked to reproduce a figure from memory (immediate recall). After a 15 min pause, the subjects were asked to reproduce the figure from memory again (delayed recall). WCST is a test for executive function or cognitive flexibility involving working memory (Berman et al., 1995). It has been shown to be sensitive to dysfunction of PFC (Nelson, 1976). In WCST, categories achieved (CA), total errors (TE) and perseverative errors of Nelson (PE) were evaluated (Lezak, 1995). In the phonemic verbal fluency test, the subject was requested to retrieve in 1 min as many words as possible beginning with the Japanese syllabic characters (hiragana) "shi," "i" and "re," respectively. In the semantic verbal fluency test, the subject was requested to recall in 1 min as many words as possible belonging to a given semantic category (e.g., animals, fruit) (Lezak, 1995). RCPM was used as a general visuospatial intelligence test.

Statistical analyses. Although the selection of subjects was confined to young males in their 20's and 30's, the possible age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457, and neuropsychological performance were examined using Pearson correlation analysis. To explore the relation between D_1 and D_2 receptors and cognitive functions, linear regression between the BP_{ND} values of each ROI and each neuropsychological performance was analyzed, and the threshold for significance was set at $p = 0.05/2 = 0.025$ to correct for two regions (PFC and HPC). Although a single dominant factor underlying the scores on all tests, i.e., general cognitive ability, might contribute to intercorrelations across the tests, what we measure with neuropsychological tests is, by nature, a dimensionality of cognitive ability. Therefore, correction of p values for multiple comparisons was done only for regions, not for multiple neuropsychological tests. To examine putative nonlinear (inverted U-shaped) relations between prefrontal dopamine receptors and frontal lobe functions, quadratic regression between the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and neuropsychological performance was analyzed by SPSS package (SPSS).

To confirm the findings of the ROI analysis, parametric images of BP_{ND} (Gunn et al., 1997) were analyzed using statistical parametric mapping software (SPM2) (Wellcome Department of Imaging, Institute of Neurology, University College of London, London, UK). Normalized BP_{ND} images were smoothed with a Gaussian filter to 16 mm full-width

Table 1. Mean scores of neuropsychological tests and linear relations between and neuropsychological measures and BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the prefrontal cortex and hippocampus

Neuropsychological tests	Mean scores	Prefrontal cortex r (p)		Hippocampus r (p)	
		[^{11}C]SCH23390	[^{11}C]FLB457	[^{11}C]SCH23390	[^{11}C]FLB457
RALVT immediate	57.3 ± 6.2	0.07 (0.74)	0.16 (0.47)	0.10 (0.66)	0.37 (0.09)
RALVT delayed	13.0 ± 1.5	0.14 (0.53)	0.02 (0.94)	0.08 (0.72)	0.28 (0.20)
ROCFT immediate	27.7 ± 3.9	0.11 (0.63)	0.31 (0.15)	0.21 (0.34)	0.73 (p<0.001)**
ROCFT delayed	27.3 ± 4.8	0.12 (0.58)	0.38 (0.07)	0.11 (0.60)	0.67 (p<0.001)**
WCST CA	5.4 ± 1.2	0.42 (0.049)*	0.03 (0.89)	0.21 (0.33)	0.30 (0.17)
WCST TE	11.3 ± 3.7	−0.41 (0.049)*	−0.15 (0.51)	−0.30 (0.16)	−0.51 (0.01)**
WCST PE	0.8 ± 1.4	−0.27 (0.21)	−0.18 (0.42)	−0.31 (0.15)	−0.59 (0.003)**
Phonemic verbal fluency	30.9 ± 9.3	0.21 (0.35)	0.21 (0.34)	0.20 (0.36)	0.47 (0.02)**
Semantic verbal fluency	46.1 ± 7.9	−0.07 (0.76)	0.09 (0.69)	0.06 (0.77)	0.17 (0.45)
RCPM (sec)	188.5 ± 36.0	0.10 (0.65)	−0.04 (0.87)	0.11 (0.64)	0.08 (0.70)

*p < 0.05. **Significant after correction for multiple statistical tests (new significance threshold: p < 0.025[0.05/2]).

half-maximum. Using each individual cognitive performance as covariate, regression analyses with the BP_{ND} images and the covariates were performed.

Results

The mean [^{11}C]SCH23390 BP_{ND} values of PFC and HPC were 0.41 ± 0.06 (range: 0.29–0.59) and 0.33 ± 0.09 (range: 0.20–0.53), respectively. The mean [^{11}C]FLB457 BP_{ND} values of PFC and HPC were 1.16 ± 0.21 (range: 0.82–1.58) and 1.57 ± 0.28 (range: 0.98–1.92), respectively. The mean scores of the neuropsychological data are shown in Table 1. There was no age effect on the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in the two ROIs, nor on any neuropsychological performance ($p > 0.01$).

Quadratic regression analysis revealed a significant "U-shaped" relation between the BP_{ND} value of [^{11}C]SCH23390 in PFC and TE of WCST ($p < 0.001$, $r = 0.72$). (Because TE of WCST is a negative measure of frontal lobe function, the relation is not "inverted") (Fig. 1). The BP_{ND} value of [^{11}C]SCH23390 in PFC and CA of WCST also showed significant quadratic (inverted U-shaped) relation ($p < 0.001$, $r = 0.78$). However, no quadratic relation was found between the BP_{ND} value of [^{11}C]FLB 457 in PFC and any neuropsychological measures. The linear relations between neuropsychological measures and the BP_{ND} value of each ROI are shown in Table 1. As for D_1 receptors, the BP_{ND} value of [^{11}C]SCH23390 in PFC was positively correlated with CA of WCST ($p = 0.049$, $r = 0.42$), and negatively correlated with TE of WCST ($p = 0.049$, $r = -0.41$) although these relations did not survive a threshold corrected for multiple comparisons. The BP_{ND} value of [^{11}C]SCH23390 in HPC was not correlated with any neuropsychological measures. With regard to D_2 receptors, the BP_{ND} value of [^{11}C]FLB457 in HPC was positively correlated with immediate and delayed recall scores of ROCFT and phonemic verbal fluency, and negatively correlated with CA and TE of WCST. The BP_{ND} value of [^{11}C]FLB457 in PFC was not correlated with any neuropsychological measures. Figure 2 shows these relationships.

D_1 binding in PFC showed significant correlation with D_1 binding in HPC ($r = 0.74$, $p < 0.001$) and trend level correlation with D_2 binding in PFC ($r = 0.41$, $p = 0.05$), but no correlation with D_2 binding in HPC ($r = 0.27$, $p = 0.22$). D_2 binding in HPC showed significant correlation with D_2 binding in PFC ($r = 0.50$, $p = 0.02$) and trend level correlation with D_1 binding in HPC ($r = 0.36$, $p = 0.09$). D_2 binding in PFC showed no correlation with D_1 binding in HPC.

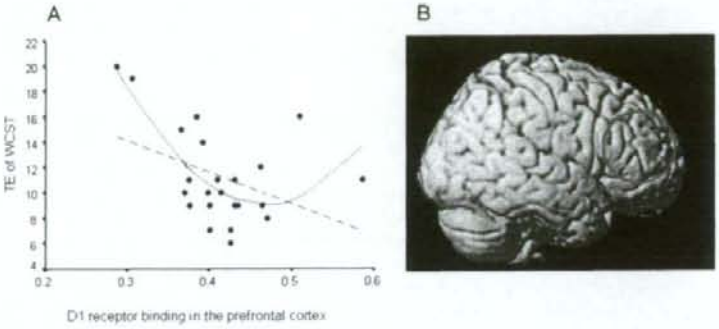

Figure 1. Quadratic (inverted U-shaped) relation between D_1 receptor binding in PFC and performance of WCST. ***A***, ROI analysis revealed a significant quadratic regression between the BP_{ND} value of [^{11}C]SCH23390 in PFC ($BP_{D1\,PFC}$) and TE of WCST. Red solid line, quadratic regression; black broken line, linear regression. Based on ROI analysis, the relation between $BP_{D1\,PFC}$ and TE can be expressed as follows: $TE = 326.92(BP_{D1\,PFC} - 0.47)^2 + 9.10$. ***B***, Using this equation, SPM analysis also revealed a significant quadratic regression between prefrontal D_1 receptor binding and TE of WCST ($p < 0.001$, uncorrected, extent threshold >30 voxels).

Using SPM2, we conduced standard voxel-based morphometry without modulation (Ashburner and Friston, 2000) to test whether the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC were related to the prefrontal and hippocampal gray matter concentration in the normalized images, respectively. The age and total gray matter (GM) volume were treated as confounding covariates in an analysis of covariance. The total GM volume was given by the total number of voxels within the GM compartment of each subject. The analysis revealed that there were no significant correlations between the BP values of [^{11}C]SCH23390 and [^{11}C]FLB457 in PFC and HPC and the concentration of gray matter in the prefrontal and hippocampal regions, respectively, at a threshold of $p = 0.01$, uncorrected.

Discussion

Although D_1 receptor binding in PFC showed trend-level positive linear correlations with WCST performance, quadratic regression analysis revealed significant inverted U-shaped relations between D_1 receptors in PFC and WCST performance. That is, a too high or too low level of D_1 receptor expression in PFC leads to high errors and a low number of categories achieved. However, D_2 receptor binding in PFC did not show significant relation with

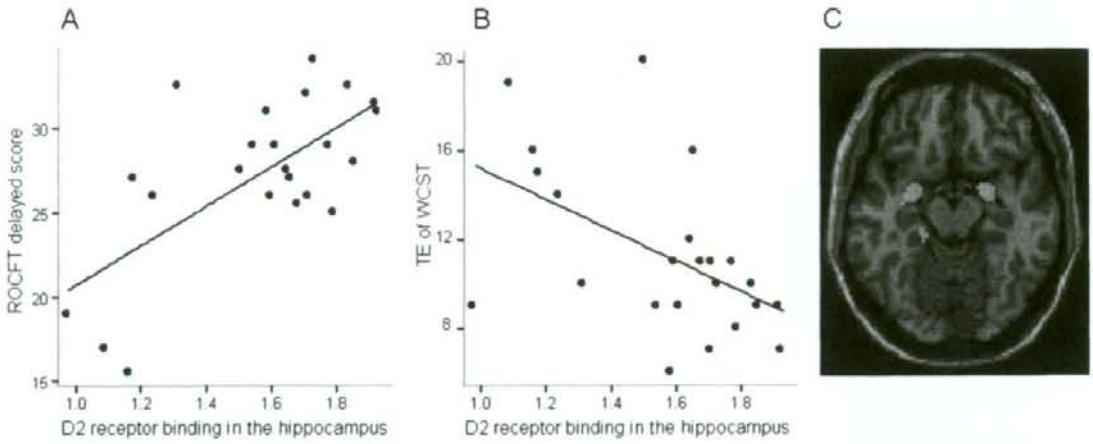

Figure 2. Correlations between D_2 receptor binding in the hippocampus and memory. ***A***, ***B***, Significant positive linear correlations between the BP_{ND} value of [^{11}C]FLB457 in the hippocampus and the delayed recall score of ROCFT and (***B***) TE of WCST revealed by ROI analysis. ***C***, The SPM result of a positive linear correlation between hippocampal D_2 receptor binding and the delayed recall score of ROCFT is shown ($p < 0.005$, uncorrected, extent threshold >30 voxels).

any neuropsychological measures. With regard to dopamine receptors in HPC, D_2 receptor binding in HPC showed positive liner correlations not only with memory function but also with frontal lobe functions, whereas D_1 receptor binding in HPC did not show significant relation with any neuropsychological measures. WCST involves a set-shifting component as well as a working memory component, although the two abilities are not mutually exclusive (Konishi et al., 1999). Working memory requires the active maintenance and manipulation of trial-unique information in a short-term memory buffer (Goldman-Rakic, 1995; Fuster, 2000). Thus, set-shifting could be regarded as updating of working memory content, and it has been demonstrated that updating of working memory content and shifting of cognitive set have a similar cognitive aspect in common (Konishi et al., 1998). Thus, in normal human subjects, the individual difference of working memory capacity could contribute to the difference in the performance of tests for cognitive flexibility.

Previous animal studies demonstrated that local injection of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994). In a human study, systemic administration of a mixed D_1/D_2 agonist, pergolide, facilitated working memory, but the selective D_2 agonist bromocriptine had no effect, indicating that the dopaminergic modulation of working memory is mediated primarily via stimulation of D_1 receptors (Müller et al., 1998). Subsequent animal studies indicated that stimulation of D_1 receptors in PFC produces an inverted U-shaped response in working memory, with the response being optimized within a narrow range of D_1 receptor stimulation (Goldman-Rakic et al., 2000; Lidow et al., 2003; Castner and Goldman-Rakic, 2004; Seamans and Yang, 2004; Vijayraghavan et al., 2007). Recent human studies have investigated the effect of a functional polymorphism in the catechol *O*-methyltransferase gene, which has been shown to modulate the prefrontal dopamine level, on prefrontal function. The results also suggested that dopamine transmission in PFC produces an inverted U-shaped response, meaning that too little or too much dopamine signaling would impair prefrontal functions, although these studies could not identify the receptor subtype that plays a central role in this effect (Mattay et al., 2003; Williams-Gray et al., 2007).

Our PET finding is the first direct evidence in human that demonstrated an inverted U-shaped relation between D_1 receptors in PFC and executive function including working memory in normal healthy subjects. Our previous PET study revealed that, compared with normal controls, D_1 receptors in PFC were decreased in schizophrenia, which was associated with poor performance on WCST (Okubo et al., 1997). However, another PET study reported that an increase in D_1 receptors in PFC was associated with working memory deficits in schizophrenia (Abi-Dargham et al., 2002). It has been discussed that these inconsistent results might stem from several factors including differences in radioligands and patient demographics. Although the reasons for these inconsistent results need to be clarified in the future, an inverted U-shaped response can account for working memory deficits in schizophrenia whether D_1 receptors in PFC are increased or decreased in patients, because the D_1 receptor inverted U-shaped response is observed within a narrow range of the normal physiological condition (Williams and Castner, 2006; Vijayraghavan et al., 2007). An inverted U-shaped response has been suggested based on cognitive and behavioral studies, but the exact physiological mechanism of this effect has not yet been fully understood. A recent monkey electrophysiology study has demonstrated a neuron-level mechanism that constitutes the inverted U-shaped response whereby too much or too little stimulation of prefrontal D_1 receptors leads to working memory deficits. D_1 receptor stimulation had a suppressive effect on the PFC neural activities involved in a spatial working memory task. Moderate D_1 receptor stimulation spatially tunes PFC neurons that process target signals by preferentially suppressing nontarget (noisy) neural activities, whereas excessive D_1 receptor stimulation induces nonselective suppression of PFC neural activities regardless of whether the neural activities are task-related or not (Vijayraghavan et al., 2007).

Animal studies have suggested that the inverted U-shaped principle of D_1 receptor stimulation mediating working memory does not necessarily apply to other prefrontal functions (Floresco and Magyar, 2006). Therefore, it is noteworthy that prefrontal D_1 receptors were not associated with other prefrontal measures besides WCST, because fluency task by phonetic or semantic cues

and problem-solving test with visuospatial analysis are less dependent on the working memory process.

Considering that D_1 binding in PFC was not correlated significantly with D_2 binding either in PFC or HPC, D_1- and D_2-mediated working memory processes are considered to contribute differently to the completion of WCST. Although previous animal studies showed that working memory or executive function mainly depends on D_1 receptors, not on D_2 receptors in PFC (Sawaguchi and Goldman-Rakic, 1994; Seamans et al., 1998), a recent rat study demonstrated that D_2 receptors in PFC were necessary for set-shifting ability (Floresco et al., 2006). It has been suggested that when the dopamine level is high under a novel circumstance, the prefrontal network is mainly modulated by D_2 receptors. In such state, the network is likely to process multiple information (Seamans and Yang, 2004; Floresco et al., 2006). During the set-shifting stage of WCST, one needs to disengage from the previous strategy and compare alternative options under a new condition. After shifting attentional sets, one needs to learn and maintain a new strategy of WCST. In such condition, the dopamine level is considered to be moderate and D_1 receptors play a central role in stabilizing the network (Seamans and Yang, 2004; Floresco et al., 2006). We did not find any correlation between D_2 binding in PFC and WCST performances, possibly attributable to the fact that the working memory component and the set-shifting component are not entirely dissociable in WCST (Konishi et al., 1999). Instead, D_2 binding in HPC was related to WCST performances. Although the role of hippocampal D_2 receptors in set-shifting is not known, a possible interpretation is that in the initial set-shifting stage of WCST, D_2 receptors in HPC might play a role in quick learning and comparison to guide future behaviors, and once a new strategy is learned, D_1 receptors in PFC might contribute to the stability and maintenance of the novel strategy.

The association between hippocampal D_2 receptors and memory is consistent with the findings of previous PET studies (Kemppainen et al., 2003; Takahashi et al., 2007). The finding that hippocampal D_2 binding was more related to visuospatial memory than to verbal memory might stem from the fact that verbal learning is dependent on regions other than HPC, such as anterior, lateral and superior temporal lobes, which are involved in human language, although HPC plays a central role in both types of memory (Hodges and Graham, 2001). Umegaki et al. (2001) reported that injection of a D_2 receptor antagonist into HPC impaired memory performance and that the memory impairment was ameliorated by coinjection of a D_2 receptor agonist. They also found that local infusion of D_2 agonist into HPC stimulated acetylcholine release in HPC and ameliorated scopolamine-induced memory impairment (Fujishiro et al., 2005). In addition, hippocampal D_2 receptors appear to be involved in synaptic plasticity. It has been reported that D_2 antagonist inhibited long-term potentiation in HPC (Frey et al., 1990; Manahan-Vaughan and Kulla, 2003), the key mechanism underlying memory consolidation (Jay, 2003; Lynch, 2004). There is some evidence from animal studies that hippocampal D_1 receptors are also involved in memory (Hersi et al., 1995a,b; Bach et al., 1999), but supporting our PET data, Wilkerson and Levin (1999) reported that hippocampal D_1 receptors were not as responsible as D_2 receptors for memory functions.

In line with our previous study (Takahashi et al., 2007), we also found hippocampal D_2 receptors to be involved in the performance of WCST and phonemic verbal fluency, which is more dependent on PFC than semantic verbal fluency. Patients with lesions in HPC sometimes show deficits in WCST (Corkin, 2001; Igarashi et al., 2002). These observations suggest that hippocampal D_2 receptors could modulate PFC activity by the HPC–PFC pathway, which plays a significant role in the cognitive process (Laroche et al., 2000; Thierry et al., 2000). Accumulating evidence has suggested the modulatory effects of dopamine on HPC–PFC interactions (Seamans et al., 1998; Aalto et al., 2005; Tseng et al., 2007; Goto and Grace, 2008). Conceivably, dopamine influences PFC neurons directly by prefrontal D_1 receptors and indirectly by hippocampal D_2 receptors via the HPC–PFC pathway.

Müller et al. (1998) reported that the systemic administration of the mixed D_1/D_2 agonist pergolide facilitated working memory, whereas selective D_2 agonist had no effect. However, there is converging evidence from human and animal studies to suggest the involvement of D_2 receptors in cognitive functions. It was reported that the systemic administration of D_2 agonist in human improved cognitive functions including working memory and executive functions (McDowell et al., 1998), and the administration of D_2 antagonist impaired those functions (Mehta et al., 1999). In an animal study, it was reported that mice lacking D_2 receptors showed a working memory deficit (Glickstein et al., 2002). These studies, however, did not reveal the regions most responsible for these effects. Moreover, although the involvement of D_1 receptors in working memory is widely recognized, it was not clear whether D_1 receptor stimulation alone or the combination of D_1 and D_2 receptor stimulation is most effective. Our finding suggested that orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for executive functions including working memory.

The current study has several limitations. First, although BP_{ND} is the complex value of receptor density and affinity (the inverse of Kd), previous studies indicated that the affinity does not differ according to region (Suhara et al., 1999) and that extrastriatal binding of current PET ligands is not sensitive to endogenous dopamine (Abi-Dargham et al., 1999; Okauchi et al., 2001). Still, we should keep in mind that the BP_{ND} values of [^{11}C]SCH23390 and [^{11}C]FLB457 might not necessarily be equivalents for D_1 and D_2 receptor functions, respectively. This emphasizes the need for PET investigations of the relation of BP_{ND} and presynaptic function or second messenger beyond dopamine receptors. Alternatively, multimodal imaging study combining the current method with other modalities such as functional MRI might also be advantageous in investigating the direct relation between dopamine receptor function and PFC functions. Second, we measured the level of dopamine receptor binding during a resting state rather than during cognitive tasks. It is difficult to measure endogenous dopamine release in extrastriatal regions with the current PET ligands (Abi-Dargham et al., 1999; Okauchi et al., 2001). Future study with radioligands more sensitive to endogenous dopamine release will enable us to examine its degree of receptor occupancy. Finally, attributable to limitations of the [^{11}C] radioligand, the data of [^{11}C] FLB457 binding in the striatum was not available. The striatum plays an important role in the prefrontal-hippocampus pathway. PET data in the striatum would lead to a better understanding of the interaction of these three regions. Future study with triple radioligands such as [^{11}C]SCH23390, [^{11}C] FLB457 and [^{11}C] raclopride will enable us to examine striatal and extrastriatal D_1 and D_2 receptors in the same subject.

In summary, we found that an inverted U-shaped relation existed between D_1 receptor binding in PFC and WCST performance, indicating an inverted U-shaped relation between prefrontal D_1 receptors and working memory, and that prefrontal D_2 receptor binding was not related to any frontal lobe functions.

Hippocampal D_2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside HPC (frontal lobe functions), which are mainly subserved by PFC, via the HPC–PFC pathway. Our findings suggest that prefrontal D_1 receptors and hippocampal D_2 receptors might be targets for pharmacological therapeutics for cognitive and memory impairments observed in neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease and schizophrenia.

References

Aalto S, Brück A, Laine M, Någren K, Rinne JO (2005) Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D_2 receptor ligand [^{11}C]FLB 457. J Neurosci 25:2471–2477.

Abi-Dargham A, Simpson N, Kegeles L, Parsey R, Hwang DR, Anjilvel S, Zea-Ponce Y, Lombardo I, Van Heertum R, Mann JJ, Foged C, Halldin C, Laruelle M (1999) PET studies of binding competition between endogenous dopamine and the D1 radiotracer [11C]NNC 756. Synapse 32:93–109.

Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M (2002) Prefrontal dopamine D_1 receptors and working memory in schizophrenia. J Neurosci 22:3708–3719.

Ashburner J, Friston KJ (2000) Voxel-based morphometry–the methods. Neuroimage 11:805–821.

Bach ME, Barad M, Son H, Zhuo M, Lu YF, Shih R, Mansuy I, Hawkins RD, Kandel ER (1999) Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. Proc Natl Acad Sci U S A 96:5280–5285.

Berman KF, Ostrem JL, Randolph C, Gold J, Goldberg TE, Coppola R, Carson RE, Herscovitch P, Weinberger DR (1995) Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. Neuropsychologia 33:1027–1046.

Castner SA, Goldman-Rakic PS (2004) Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D_1 receptor stimulation. J Neurosci 24:1446–1450.

Corkin S (2001) Beware of frontal lobe deficits in hippocampal clothing. Trends Cogn Sci 5:321–323.

Farde L, Halldin C, Stone-Elander S, Sedvall G (1987) PET analysis of human dopamine receptor subtypes using 11C-SCH 23390 and 11C-raclopride. Psychopharmacology (Berl) 92:278–284.

Floresco SB, Magyar O (2006) Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berl) 188:567–585.

Floresco SB, Magyar O, Ghods-Sharifi S, Vexelman C, Tse MT (2006) Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. Neuropsychopharmacology 31:297–309.

Frey U, Schroeder H, Matthies H (1990) Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. Brain Res 522:69–75.

Fujishiro H, Umegaki H, Suzuki Y, Oohara-Kurotani S, Yamaguchi Y, Iguchi A (2005) Dopamine D2 receptor plays a role in memory function: implications of dopamine-acetylcholine interaction in the ventral hippocampus. Psychopharmacology (Berl) 182:253–261.

Fuster JM (2000) Executive frontal functions. Exp Brain Res 133:66–70.

Glickstein SB, Hof PR, Schmauss C (2002) Mice lacking dopamine D_2 and D_3 receptors have spatial working memory deficits. J Neurosci 22:5619–5629.

Goldman-Rakic PS (1995) Cellular basis of working memory. Neuron 14:477–485.

Goldman-Rakic PS, Muly EC 3rd, Williams GV (2000) D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 31:295–301.

Goto Y, Grace AA (2008) Dopamine modulation of hippocampal prefrontal cortical interaction drives memory-guided behavior. Cereb Cortex 18:1407–1414.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997) Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 6:279–287.

Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994) Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology 11:245–256.

Halldin C, Farde L, Högberg T, Mohell N, Hall H, Suhara T, Karlsson P, Nakashima Y, Swahn CG (1995) Carbon-11-FLB 457: a radioligand for extrastriatal D2 dopamine receptors. J Nucl Med 36:1275–1281.

Hersi AI, Rowe W, Gaudreau P, Quirion R (1995a) Dopamine D1 receptor ligands modulate cognitive performance and hippocampal acetylcholine release in memory-impaired aged rats. Neuroscience 69:1067–1074.

Hersi AI, Richard JW, Gaudreau P, Quirion R (1995b) Local modulation of hippocampal acetylcholine release by dopamine D_1 receptors: a combined receptor autoradiography and *in vivo* dialysis study. J Neurosci 15:7150–7157.

Hodges JR, Graham KS (2001) Episodic memory: insights from semantic dementia. Philos Trans R Soc Lond B Biol Sci 356:1423–1434.

Igarashi K, Oguni H, Osawa M, Awaya Y, Kato M, Mimura M, Kashima H (2002) Wisconsin card sorting test in children with temporal lobe epilepsy. Brain Dev 24:174–178.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, et al. (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539.

Jay TM (2003) Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. Prog Neurobiol 69:375–390.

Kemppainen N, Laine M, Laakso MP, Kaasinen V, Någren K, Vahlberg T, Kurki T, Rinne JO (2003) Hippocampal dopamine D2 receptors correlate with memory functions in Alzheimer's disease. Eur J Neurosci 18:149–154.

Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, Miyashita Y (1998) Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat Neurosci 1:80–84.

Konishi S, Kawazu M, Uchida I, Kikyo H, Asakura I, Miyashita Y (1999) Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin Card Sorting Test. Cereb Cortex 9:745–753.

Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158.

Laroche S, Davis S, Jay TM (2000) Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. Hippocampus 10:438–446.

Lezak MD (1995) Neuropsychological assesment. Ed 3. New York: Oxford UP.

Lidow MS, Koh PO, Arnsten AF (2003) D1 dopamine receptors in the mouse prefrontal cortex: Immunocytochemical and cognitive neuropharmacological analyses. Synapse 47:101–108.

Lynch MA (2004) Long-term potentiation and memory. Physiol Rev 84:87–136.

Manahan-Vaughan D, Kulla A (2003) Regulation of depotentiation and long-term potentiation in the dentate gyrus of freely moving rats by dopamine D2-like receptors. Cereb Cortex 13:123–135.

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 100:6186–6191.

McDowell S, Whyte J, D'Esposito M (1998) Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain 121:1155–1164.

Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW (1999) Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology (Berl) 146:162–174.

Müller U, von Cramon DY, Pollmann S (1998) D_1- versus D_2-receptor modulation of visuospatial working memory in humans. J Neurosci 18:2720–2728.

Nelson HE (1976) A modified card sorting test sensitive to frontal lobe defects. Cortex 12:313–324.

Okauchi T, Suhara T, Maeda J, Kawabe K, Obayashi S, Suzuki K (2001) Effect of endogenous dopamine on extrastriatal [(11)C]FLB 457 binding measured by PET. Synapse 41:87–95.

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997) Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 385:634–636.

Olsson H, Halldin C, Swahn CG, Farde L (1999) Quantification of [11C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. J Cereb Blood Flow Metab 19:1164–1173.

Sawaguchi T, Goldman-Rakic PS (1994) The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J Neurophysiol 71:515–528.

Seamans JK, Yang CR (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 74:1–58.

Seamans JK, Floresco SB, Phillips AG (1998) D_1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J Neurosci 18:1613–1621.

Suhara T, Sudo Y, Okauchi T, Maeda J, Kawabe K, Suzuki K, Okubo Y, Nakashima Y, Ito H, Tanada S, Halldin C, Farde L (1999) Extrastriatal dopamine D2 receptor density and affinity in the human brain measured by 3D PET. Int J Neuropsychopharmcol 2:73–82.

Takahashi H, Kato M, Hayashi M, Okubo Y, Takano A, Ito H, Suhara T (2007) Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. Neuroimage 34:1643–1649.

Thierry AM, Gioanni Y, Dégénétais E, Glowinski J (2000) Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. Hippocampus 10:411–419.

Tseng KY, Lewis BL, Lipska BK, O'Donnell P (2007) Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. Biol Psychiatry 62:730–738.

Umegaki H, Munoz J, Meyer RC, Spangler EL, Yoshimura J, Ikari H, Iguchi A, Ingram DK (2001) Involvement of dopamine D(2) receptors in complex maze learning and acetylcholine release in ventral hippocampus of rats. Neuroscience 103:27–33.

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 10:376–384.

Wilkerson A, Levin ED (1999) Ventral hippocampal dopamine D1 and D2 systems and spatial working memory in rats. Neuroscience 89:743–749.

Williams GV, Castner SA (2006) Under the curve: critical issues for elucidating D1 receptor function in working memory. Neuroscience 139:263–276.

Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker RA (2007) Catechol *O*-methyltransferase $Val^{158}Met$ genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci 27:4832–4838.

knockout mouse (*27*). [^{125}I]IAF photolabeling of liver homogenates from wild-type (WT) and sigma-1 receptor knockout (KO) mice indeed showed the absence of sigma-1 receptor (26 kD) in the KO samples (Fig. 3A). In WT neonatal cardiac myocytes, 100 μM DMT reversibly inhibited I_{Na} by 29 ± 3% (n = 7 WT myocytes), whereas I_{Na} was reduced by only 7 ± 2% (n = 7 KO myocytes) in KO myocytes (Fig. 3C, $P < 0.002$).

Both DMT and sigma receptor ligands influence animal behavior. DMT injection induces hypermobility in rodents concurrently treated with the monoamine oxidase inhibitor pargyline (*28*), and this action is not antagonized by blockers of dopamine or serotonin receptors, but is potently inhibited by haloperidol (*28*). Although haloperidol is thought to act in part through the dopamine D_2 receptor system, it is also a potent sigma-1 receptor agonist [sigma-1 inhibition constant (K_i) = 3 nM (*29*); sigma-2 K_i = 54 nM (*29*)] when inhibiting voltage-gated ion channels (*5*, *25*). Haloperidol reduces brain concentrations of DMT (*8*) and DMT inhibits haloperidol binding in brain tissue more robustly than the dopamine agonist apomorphine (*8*). On the basis of these findings, which were discovered before sigma receptor identification, DMT has been hypothesized to act through an unknown "hallucinogen" receptor (*8*). We confirmed results (*28*) that intraperitoneal (ip) administration of DMT (2 mg per kilogram of body weight) 2 hours after pargyline (75 mg/kg, ip) injection induced hypermobility in WT mice (7025 ± 524.1 cm, n = 12 WT mice) in an open-field assay. Identical drug treatments in sigma-1 receptor KO mice had no hypermobility action (2328 ± 322.9 cm, n = 12 KO mice, $P < 0.0001$; Fig. 4, A and B). This result is particularly important to our understanding of sigma-1 receptor biological function because the KO mice are viable and fertile (*27*). The sigma-1 receptor dependence of DMT-induced hypermobility parallels that induced by the sigma-1 receptor ligand (+)-SKF10047 in WT but not in KO mice (*27*). As a positive control, methamphetamine, which is thought to act through catecholaminergic systems, induced hypermobility in both WT and KO mice (3 mg/kg, ip, n = 6 mice; Fig. 4, B and C) with a reduced onset rate compared with that seen for DMT (Fig. 4, A and C). This indicates that behavioral actions of DMT depend on the sigma-1 receptor, which may provide an alternative research area for psychiatric disorders that have not been linked to dopamine or *N*-methyl-D-aspartate systems.

The binding, biochemical, physiological, and behavioral studies reported here all support the hypothesis that DMT acts as a ligand for the sigma-1 receptor. On the basis of our binding results and the sigma-1 receptor pharmacophore, endogenous trace amines and their *N*-methyl and *N*,*N*-dimethyl derivatives are likely to serve as endogenous sigma receptor regulators. Moreover, DMT, the only known mammalian *N*,*N*-dimethylated trace amine, can activate the sigma-1 receptor to modulate Na^+ channels. The recent discovery that the sigma-1 receptor functions as a molecular chaperone (*30*) may be relevant, because sigma-1 receptors, which are observed in the endoplasmic reticulum, associate with plasma membrane Kv 1.4 channels (*22*) and may serve as a molecular chaperone for ion channels. Furthermore, the behavioral effect of DMT may be due to activation or inhibition of sigma-1 receptor chaperone activity instead of, or in addition to, DMT/sigma-1 receptor modulation of ion channels. These studies thus suggest that this natural hallucinogen could exert its action by binding to sigma-1 receptors, which are abundant in the brain (*1*, *27*). This discovery may also extend to *N*,*N*-dimethylated neurotransmitters such as the psychoactive serotonin derivative *N*,*N*-dimethylserotonin (bufotenine), which has been found at elevated concentrations in the urine of schizophrenic patients (*10*). The finding that DMT and sigma-1 receptors act as a ligand-receptor pair provides a long-awaited connection that will enable researchers to elucidate the biological functions of both of these molecules.

References and Notes

1. T. Hayashi, T. P. Su, *CNS Drugs* **18**, 269 (2004).
2. P. Bouchard *et al.*, *Eur. J. Neurosci.* **7**, 1952 (1995).
3. T. P. Su, A. D. Weissman, S. Y. Yeh, *Life Sci.* **38**, 2199 (1986).
4. T. P. Su, E. D. London, J. H. Jaffe, *Science* **240**, 219 (1988).
5. R. A. Wilke *et al.*, *J. Physiol.* **517**, 391 (1999).
6. R. A. Glennon *et al.*, *J. Med. Chem.* **37**, 1214 (1994).
7. F. F. Moebius, R. J. Reiter, M. Hanner, H. Glossmann, *Br. J. Pharmacol.* **121**, 1 (1997).
8. S. A. Barker, J. A. Monti, S. T. Christian, *Int. Rev. Neurobiol.* **22**, 83 (1981).
9. F. Franzen, H. Gross, *Nature* **206**, 1052 (1965).
10. M. S. Jacob, D. E. Presti, *Med. Hypotheses* **64**, 930 (2005).
11. J. Axelrod, *Science* **134**, 343 (1961).
12. J. M. Saavedra, J. Axelrod, *Science* **175**, 1365 (1972).
13. J. M. Beaton, P. E. Morris, *Mech. Ageing Dev.* **25**, 343 (1984).
14. S. A. Burchett, T. P. Hicks, *Prog. Neurobiol.* **79**, 223 (2006).
15. B. Borowsky *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 8966 (2001).
16. L. Lindemann *et al.*, *Genomics* **85**, 372 (2005).
17. J. R. Kahoun, A. E. Ruoho, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 1393 (1992).
18. A. Pal *et al.*, *Mol. Pharmacol.* **72**, 921 (2007).
19. Y. Chen, A. R. Hajipour, M. K. Sievert, M. Arbabian, A. E. Ruoho, *Biochemistry* **46**, 3532 (2007).
20. P. J. Lupardus *et al.*, *J. Physiol.* **526**, 527 (2000).
21. H. Zhang, J. Cuevas, *J. Pharmacol. Exp. Ther.* **313**, 1387 (2005).
22. E. Aydar, C. P. Palmer, V. A. Klyachko, M. B. Jackson, *Neuron* **34**, 399 (2002).
23. R. A. Wilke *et al.*, *J. Biol. Chem.* **274**, 18387 (1999).
24. C. Kennedy, G. Henderson, *Neuroscience* **35**, 725 (1990).
25. H. Zhang, J. Cuevas, *J. Neurophysiol.* **87**, 2867 (2002).
26. M. A. Johannessen, A. Ramos-Serrano, S. Ramachandran, A. E. Ruoho, M. B. Jackson, "Sigma receptor modulation of voltage-dependent sodium channels," Program No. 466.22, Annual Neuroscience Meeting, San Diego, CA, 5 November 2007.
27. F. Langa *et al.*, *Eur. J. Neurosci.* **18**, 2188 (2003).
28. P. Jenner, C. D. Marsden, C. M. Thanki, *Br. J. Pharmacol.* **69**, 69 (1980).
29. R. R. Matsumoto, B. Pouw, *Eur. J. Pharmacol.* **401**, 155 (2000).
30. T. Hayashi, T. P. Su, *Cell* **131**, 596 (2007).

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Supporting Online Material

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Materials and Methods
Fig. S1 and scheme S2
References

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When Your Gain Is My Pain and Your Pain Is My Gain: Neural Correlates of Envy and Schadenfreude

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We often evaluate the self and others from social comparisons. We feel envy when the target person has superior and self-relevant characteristics. Schadenfreude occurs when envied persons fall from grace. To elucidate the neurocognitive mechanisms of envy and schadenfreude, we conducted two functional magnetic resonance imaging studies. In study one, the participants read information concerning target persons characterized by levels of possession and self-relevance of comparison domains. When the target person's possession was superior and self-relevant, stronger envy and stronger anterior cingulate cortex (ACC) activation were induced. In study two, stronger schadenfreude and stronger striatum activation were induced when misfortunes happened to envied persons. ACC activation in study one predicted ventral striatum activation in study two. Our findings document mechanisms of painful emotion, envy, and a rewarding reaction, schadenfreude.

Envy is one of the seven biblical sins, the Shakespearian "green-eyed monster," and what Bertrand Russell (*1*) called an unfortunate facet of human nature. It is an irrational, unpleasant feeling and a "painful emotion" (*2*) characterized by feelings of inferiority and resentment produced by an awareness of another's superior quality, achievement, or possessions (*3*). Understanding envy is important because of its broad implications, ranging from individual mat-

ters to social problems. It concerns personal life satisfaction (*4*), self-evaluation/maintenance (*5*), and economic and political issues (*6–8*). We judge objects more by comparison than by their intrinsic worth and value (*9*), and self-evaluations are often derived from social comparisons with people who are self-relevant, sharing similar attributes, characteristics, group memberships, and interests (for example, gender, age, and social class) (*10*).

When envy is evoked, we often have a desire to possess the same advantage or may wish that the other lacks it (*3*). When misfortune occurs to others, emotions can manifest themselves in several ways. We can sympathize and have feelings of concern and sorrow for the other person (*11*, *12*), but we can also experience schadenfreude, a rewarding feeling derived from another's misfortune (*13*). Schadenfreude is closely related to envy, and it is more likely to arise when misfortune happens to a person who is advantaged and self-relevant than to someone who is neither advantaged nor self-relevant (*13–15*).

We investigated the brain activation associated with envy and schadenfreude. We conducted two functional magnetic resonance imaging (fMRI) studies to test two complementary hypotheses. In the first study, we hypothesized that, not only the level of possession of the person we compare ourselves with, but also the self-relevance of the comparison domain affects brain activation associated with envy through social comparison. We usually have a positive self-concept, and we experience a feeling of discomfort when we perform in a way that violates this self-concept (*16*). The anterior cingulate cortex (ACC) is activated when this positive self-concept conflicts with external information (*17*, *18*). Bearing in mind that envy is a painful emotion, we hypothesized that envy activates the dorsal ACC (dACC), where cognitive conflicts (*19*) or social pain (*12*, *20*) are processed. We predicted that dACC activation is stronger when an envied person has superior and more self-relevant possessions. In the second study, we hypothesized that a misfortune happening to an envied person produces greater brain activation associated with schadenfreude than misfortune happening to a person who is not envied. Schadenfreude should activate the ventral striatum, a central node of reward processing.

Nineteen healthy volunteers [10 men and 9 women, mean age = 22.1 ± 1.4 (SD) years] participated in the two fMRI studies. We used a scenario method as in previous social affective neuroimaging studies (*21*, *22*). Each participant was presented with a scenario in which the protagonist (oneself) and three other target persons appeared. Materials were employed from an initial survey to validate our expected results (*23*). Before the fMRI scans, we asked the participants to read and understand the scenario thoroughly and to imagine the protagonist of the scenario as themselves. In study one, we aimed to determine the level of envy in terms of whether possessions of the target person were superior or not and whether domains of comparison were self-relevant or not. In short, for male participants, the protagonist of the scenario was male and average in terms of possessions such as ability, quality, and social status. Male student A shared similar attributes with the protagonist. He possessed superior quality and ability, and the domains of comparison were important and relevant to the protagonist [superior and high relevance (SpHi)]. Female student B had different attributes and background from the protagonist. She also possessed superior quality and ability, but the domains of comparison were neither important nor relevant to the protagonist [superior and low relevance (SpLo)]. Female student C had different attributes and background from the protagonist. She possessed mediocre quality and ability, and the domains of comparison were neither important nor relevant to the protagonist [average and low relevance (AvLo)]. The scenario for male participants and profiles of the persons are shown in the appendix in (*23*). The profiles of the three target persons and comparison domains are summarized in table S1, and a schematic depiction of the stimuli and design is shown in fig. S1. We performed event-related fMRI analysis with statistical parametric mapping 2 to examine activations in response to SpHi, SpLo, and AvLo. In study two, successive misfortunes happened to student A (SpHi) and student C (AvLo) in the scenario examining reaction in response to misfortunes happening to others. A list of misfortunes is provided in table S1, and a schematic depiction of the stimuli and design is shown in fig. S2. We analyzed neural responses to misfortunes on SpHi (MisSpHi) and AvLo (MisAvLo). After the scans, the participants rated each event presented in study one in terms of how much envy they felt for the three students (i.e., 1 = no envy, 6 = extremely envious). Similarly, the participants also reported the intensity of their pleasure (schadenfreude) (1 = no pleasure, 6 = extremely pleasant) in response to misfortunes happening to students A and C in study two. That is, they gave one envy score per domain per student in study one and one schadenfreude score per misfortune per student in study two.

The self-rating results of the participants in the fMRI study were comparable to the results obtained in the initial survey. The mean values of the ratings of envy for students A, B, and C were 4.0 ± 1.0, 2.1 ± 0.8, and 1.0 ± 0.0, respectively. The mean values of schadenfreude for students A and C were

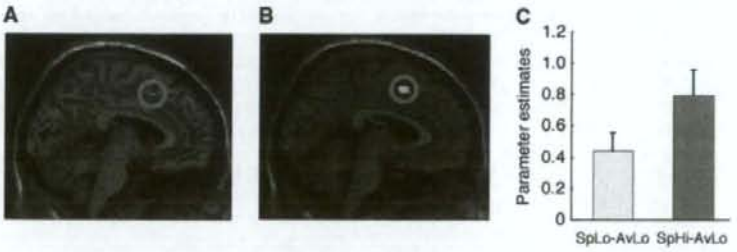

Fig. 1. Brain activation in dACC was modulated by relevance of comparison domain. Brain activations in response to **(A)** the SpLo minus AvLo condition and **(B)** the SpHi minus AvLo condition. **(C)** Mean for parameter estimates at the peak of dACC activation for SpHi-AvLo contrast (red) was greater than that for SpLo-AvLo contrast (yellow) (t = 2.56, P = 0.02). Error bars represent SE.

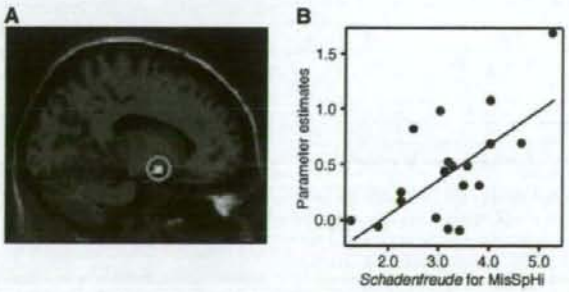

Fig. 2. Correlation between self-rating of schadenfreude and ventral striatum activation across participants. **(A)** Image showing correlation between mean rating of schadenfreude for MisSpHi and the ventral striatum in MisSpHi-MisAvLo contrast across participants. **(B)** Plots and regression line of correlation (r = 0.65, P = 0.002) between schadenfreude and parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (–14, 2, –12).

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3.3 ± 1.0 and 1.0 ± 0.0, respectively. Self-rating scores of envy for student A were positively correlated with the magnitude of schadenfreude for student A (correlation coefficient $r = 0.50$, $P = 0.03$). Both SpHi-AvLo and SpLo-AvLo conditions produced activations in dACC, a region implicated in the processing of conflict or pain, but dACC activation was greater in the SpHi-AvLo condition ($x = -4$, $y = 8$, $z = 54$, z score = 4.07) than in the SpLo-AvLo condition ($x = -4$, $y = 16$, $z = 46$, Z score = 3.65) (Fig. 1, A to C). Regression analysis revealed positive linear correlation between self-rating scores of envy and the degree of activation in the dACC ($x = -2$, $y = 10$, $z = 52$, z score = 4.36) in SpHi-AvLo contrast (fig. S3, A and B). The MisSpHi-MisAvLo condition produced activations in the reward-related regions: the dorsal striatum (caudate, putamen) ($x = -16$, $y = -2$, $z = 16$, z score = 4.44), the ventral striatum including the nucleus accumbens ($x = -12$, $y = 6$, $z = -10$, z score = 4.41), and the medial orbitofrontal cortex ($x = -8$, $y = 54$, $z = -10$, z score = 3.46) (fig. S4, A and B). There was correlation between the intensity of schadenfreude and the degree of activation in the ventral striatum ($x = -14$, $y = 2$, $z = -12$, z score = 3.98) in MisSpHi-MisAvLo contrast (Fig. 2, A and B). dACC ($x = -2$, $y = 10$, $z = 52$) activation in SpHi-AvLo contrast was positively correlated with ventral striatum ($x = -14$, $y = 2$, $z = -12$) activation in MisSpHi-MisAvLo contrast (Fig. 3).

This study investigated the neurocognitive mechanisms of envy and schadenfreude and the role of social comparison in the central processing of these emotions. At the behavioral level in study one, the intensity of envy is modulated by the quality of the possession of the person we compare with and the self-relevance of the comparison domain. That is, if the possession of the target person is superior and the comparison domain is self-relevant, we feel intense envy.

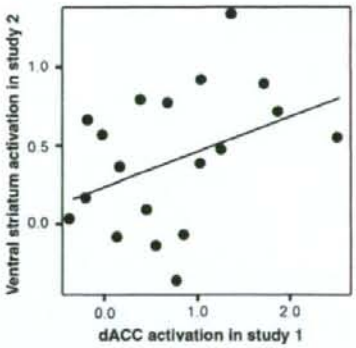

Fig. 3. Relation between dACC activation associated with envy and ventral striatum activation associated with schadenfreude. The x axis indicates the parameter estimates of dACC activation for SpHi-AvLo contrast at a peak voxel (–2, 10, 52). The y axis indicates the parameter estimates of the ventral striatum activation for MisSpHi-MisAvLo contrast at a peak voxel (–14, 2, –12). Positive correlation between dACC activation in study one and ventral striatum activation in study two across participants is shown ($r = 0.39$, $P = 0.01$).

When the comparison domain is not self-relevant, we do not feel strong envy, even if the possession is superior. When the comparison target is neither superior nor self-relevant, we are indifferent to the target. Activation of dACC was also modulated by possession quality and self-relevance. Stronger dACC activation was observed when one felt stronger envy. Moreover, between-participant correlation analysis demonstrated that people with stronger envy showed greater activation in dACC. At the behavioral level in study two, stronger schadenfreude was related to stronger envy, and schadenfreude arose when misfortune occurred to a person who was advantaged and self-relevant. Striatal activation was observed when misfortune happened to an envied person but not when it happened to a non-envied person. Between-participant analysis revealed that people with stronger schadenfreude showed greater activation in the ventral striatum.

ACC activation in response to envy stimuli might reflect a painful feature of this emotion. It was comparable to caudal ACC activation in response to pain in the self but not to pain in others (empathic pain) (*12*), suggesting that the participants experienced a painful feeling. Activation in this region has been reported in response to social pain (distress of social exclusion) (*20*). Taken together, envy might be a social pain in the self, with feelings of being excluded from the field that one is concerned with.

We are usually motivated to maintain a positive self-concept (*16*), and we feel discomfort when our self-concept is threatened by others who outperform ourselves in a self-relevant domain. Considering the role of dACC in conflict-monitoring (*19*), the association between envy and dACC activation suggests that envy is a condition in which information recognized by social comparison conflicts with positive self-concept. Experiencing discomfort motivates us to reduce it. Discomfort arising from others outperforming us in our cherished domains can be resolved by reducing the relevance of the domain to us or changing relative performance (*16*). Students in our scenario might change their major or club at the university and, ultimately, their goals in life. Alternatively, they might make an effort to improve their own performance or possession. On the contrary, they might wish that the other lacks advantages, or they may even obstruct the advantaged student (with malice). Similarly, from an economic perspective, envy has productive and destructive effects on economic growth. It motivates the members in organizations to enhance their own performances or to sabotage their opponents' performances (*24*). When misfortune occurs to an advantaged person and contributes to narrowing the gap of relative performance in an important domain, discomfort or pain is reduced, and a pleasant feeling is induced. This pleasure at another's misfortune is correspondent to the activation of the ventral striatum and the medial orbitofrontal cortex (*25*, *26*). The striatum has also been implicated in altruistic punishment (*27*) and observing an unfair person receiving pain (*28*). Stronger dACC activation induced by the most envied student in study one predicted stronger ventral striatum activation when misfortunes occurred to the student in study two. This means that people who tend to have higher pain or conflict are more likely to have a strong pleasant feeling once they are relieved from this pain. Thus, our findings propose a neurocognitive mechanism of a psychologically rewarding reaction, schadenfreude, and its relation to envy. At the same time, ventral striatum activation without receiving an actual reward indicates that we did not evaluate objects solely by their absolute value but that social comparison plays a substantial role in evaluation (*29*).

References and Notes

1. B. Russell, *The Conquest of Happiness* (W.W. Norton, New York, 1930).
2. Aristotle, *The Art of Rhetoric* (Penguin Books, London, 1981).
3. W. G. Parrott, R. H. Smith, *J. Pers. Soc. Psychol.* **64**, 906 (1993).
4. R. H. Smith, W. G. Parrott, E. F. Diener, R. H. Hoyle, S. H. Kim, *Pers. Soc. Psychol. Bull.* **25**, 1007 (1999).
5. A. Tesser, *Adv. Exp. Soc. Psychol.* **21**, 181 (1988).
6. J. Rawls, *A Theory of Justice* (Harvard Univ. Press, Cambridge, MA, 1971).
7. R. Nozick, *Anarchy, State, and Utopia* (Basic Books, New York, 1974).
8. G. F. de la Mora, *Egalitarian Envy: The Political Foundations of Social Justice* (Paragon House, New York, 1987).
9. D. Hume, *A Treatise of Human Nature* (Oxford Univ. Press, Oxford, 1978).
10. L. Festinger, *Hum. Relat.* **7**, 117 (1954).
11. N. Eisenberg, *Novartis Found. Symp.* **278**, 71 (2007).
12. T. Singer *et al.*, *Science* **303**, 1157 (2004).
13. F. Heider, *The Psychology of Interpersonal Relations* (Wiley & Sons, New York, 1958).
14. B. de Spinoza, *The Ethics* (Biblio Bazaar, Charleston, SC, 2006).
15. W. W. van Dijk, J. W. Ouwerkerk, S. Goslinga, M. Nieweg, M. Gallucci, *Emotion* **6**, 156 (2006).
16. A. Tesser, D. Cornell, *J. Exp. Soc. Psychol.* **27**, 501 (1991).
17. D. M. Amodio *et al.*, *Psychol. Sci.* **15**, 88 (2004).
18. E. Harmon-Jones, *Biol. Psychol.* **67**, 51 (2004).
19. J. G. Kerns *et al.*, *Science* **303**, 1023 (2004).
20. N. I. Eisenberger, M. D. Lieberman, K. D. Williams, *Science* **302**, 290 (2003).
21. J. D. Greene, R. B. Sommerville, L. E. Nystrom, J. M. Darley, J. D. Cohen, *Science* **293**, 2105 (2001).
22. T. Sharot, A. M. Riccardi, C. M. Raio, E. A. Phelps, *Nature* **450**, 102 (2007).
23. Materials and methods are available as supporting material on *Science* Online.
24. E. Lazear, *J. Polit. Econ.* **97**, 561 (1989).
25. S. M. McClure, M. K. York, P. R. Montague, *Neuroscientist* **10**, 260 (2004).
26. E. Fehr, C. F. Camerer, *Trends Cogn. Sci.* **11**, 419 (2007).
27. D. J.-F. de Quervain *et al.*, *Science* **305**, 1254 (2004).
28. T. Singer *et al.*, *Nature* **439**, 466 (2006).
29. K. Fliessbach *et al.*, *Science* **318**, 1305 (2007).

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 to S4
Table S1

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Regular Article

Hyperfrontality in patients with schizophrenia during saccade and antisaccade tasks: A study with fMRI

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Aims: Antisaccadic eye movements, requiring inhibition of a saccade toward a briefly appearing peripheral target, are known to be impaired in schizophrenia. Previous neuroimaging studies have indicated that patients with schizophrenia show diminished activations in the frontal cortex and basal ganglia. These studies used target fixation as a baseline condition. However, if the levels of brain activities at baseline are not compatible between patients and healthy subjects, between-group comparison on antisaccade-related activations is consequently invalidated. One possibility is that patients with schizophrenia may present with greater activation during fixation than healthy subjects. In order to examine this possibility, here we investigated brain activities associated with antisaccade in the two groups without using target fixation at baseline.

Methods: Functional brain images were acquired during prosaccades and antisaccades in 18 healthy subjects and 18 schizophrenia patients using a boxcar functional magnetic resonance imaging design. Eye movements were measured during scanning.

Results: In the patient group, the elevated activities in the dorsolateral prefrontal cortex (DLPFC) and thalamus, normally seen in antisaccade tasks relative to saccade tasks, were no longer observed. Moreover, in normal subjects, activities in the DLPFC and thalamus were greater during the antisaccade task than during the saccade task. In patients, no such difference was observed between the two tasks, suggesting that these brain regions are likely to be highly activated even by a simple task such as fixation. In particular, the DLPFC and thalamus in patients were not activated at a level commensurate with the difficulty of the tasks presented.

Conclusions: From these results, it is suggested that schizophrenia entails dysfunctions in the fronto-striato-thalamo-cortical network associated with motor function control.

Key words: antisaccade, fMRI, hyperfrontality, saccade, schizophrenia.

SACCADIC EYE MOVEMENTS are the primary mechanism used by primates to visually explore their environments. A visually guided reflexive saccade can be defined as an automatic orienting response to a novel visual target in the peripheral field. Patients with schizophrenia perform prosaccades normally, making rapid and accurate eye movements to targets.[1–3] In contrast, the inhibition of

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automatic saccades is impaired in schizophrenic patients.[4] One task used to investigate saccade inhibition is the antisaccade task, which requires subjects to inhibit a saccade toward a briefly appearing peripheral target, and to instead immediately generate a saccade to a point in the opposite direction.[5] Antisaccade deficits have high sensitivity and high specificity for the diagnosis of schizophrenia and are thought to be a genetic marker for the illness. Reported rates of antisaccade deficits range from 24% to 71% in patients with schizophrenia and from 2% to 27% in normal controls.[6–9]

Several comparison studies to date have examined the brain regions associated with antisaccade tasks in schizophrenic patients and normal control subjects.[10–12] Most of these have reported reduced activity in the basal ganglia and the cortex, including the prefrontal area, in the schizophrenic group. As we will discuss further below, we question whether the activities of these brain regions were in fact reduced or not. Functional magnetic resonance imaging (fMRI) is a specialized MRI scan that measures hemodynamic responses related to neural activity in the brain. When two actions that generate neural activity are compared in fMRI, an analysis is based on the difference between a baseline signal and a signal measured at the time of task execution. Therefore, when comparing two groups, it is important to be able to assume that the baseline levels in the two groups are equivalent. Most previous fMRI research on antisaccade and saccade tasks used a target that required subjects to focus on a central fixation point during baseline imaging. One possibility is that patients with schizophrenia may exhibit greater cerebral activities during the fixation condition than healthy subjects. In order to examine this baseline effect, here we compared schizophrenic patients and normal subjects using a blank screen on which subjects were not required to focus at baseline.

MATERIALS AND METHODS

Subjects

Eighteen patients with schizophrenia (11 men and 7 women; mean age 34.8 ± 7.9) and 18 healthy subjects (9 men and 9 women; mean age 37.6 ± 4.8) participated in this study. All patients met the criteria for schizophrenia according to the DSM-IV. The mean duration of education was significantly longer ($P < 0.05$) in the healthy subject group than in the schizophrenia group. In the latter group, the mean age at onset of psychosis was 25.8 years old, the mean Brief Psychiatric Rating Scale total score was 41.9, and the mean total dose of antipsychotic medication per patients converted to haloperidol equivalency was 16.0 mg. All healthy subjects were free from neurological or psychiatric illness, and no abnormalities were observed on brain structural MRI. Written informed consent was obtained from all participants. All participants were right-handed according to the Edinburgh Handedness Inventory.[13] This project was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Nihon University School of Medicine.

MRI acquisition

MRI data were acquired using a 1.5T Siemens Symphony system (Siemens, Erlangen, Germany). Gradient-recalled echo planar imaging (EPI) was used for the fMRI sequence to obtain blood oxygen level-dependent contrast. Interleaved multi-slice gradient EPI was used to produce 40 continuous, 3-mm thick axial slices encompassing the entire brain (echo time = 62 ms, repetition time = 4000 ms, flip angle = 90 degrees, field of view = 192 mm, 64•64 matrix). Each series comprised 104 scans with a complete duration of 416 s. The run began with four dummy volumes to allow for T1 equilibration effects. The head of the subject was fixed using cushions to minimize motion artifacts.

Behavioral methods

Saccade and antisaccade performance was recorded outside of the magnet. Horizontal and vertical eye movements and target position were measured using electro-oculography (EOG) (NEC) and a goggles-type display (SONY).

Stimulus projection

The stimulus was generated using a personal computer (OS: Windows 98) and made to order software. The stimulus was projected on a small screen attached to a head coil, using a liquid crystal display projector system customized to our MRI machine (Kiyohara Optics, Tokyo).

Prosaccade task

Each trial began with the target in central fixation (0 degrees) for a random duration of 500–1500 ms.

The target then shifted randomly to left or right horizontal peripheral locations (10 degrees from the center position), where it remained for 1000 ms. The target size was 1 degree of the visual angle. The number of left and right saccadic eye movements was the same. Participants were instructed to follow the target as quickly and accurately as possible, alternating between 40 s of control condition task and 40 s of prosaccade condition, completing 10 sets of trials in all. During the baseline condition, subjects were in total darkness and were asked to maintain fixation and not blink.

Antisaccade task

The parameters for the antisaccade task were identical to those for the prosaccade task. The antisaccade task required participants to fixate the target in the central position and to redirect their gaze in the opposite direction of the target as soon as it shifted to the periphery. Participants performed 10 sets of trials in total, alternating antisaccade and control conditions.

fMRI data analysis

Image analysis was performed using an Ultra5 workstation (Sun Microsystems, Palo Alto, CA, USA) using MATLAB (Mathworks Inc., Natick, MA, USA) and statistical mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Before statistical parametric maps were calculated, EPI images for each time series were realigned to the first functional image to remove residual head movement. Images were then coregistered and normalized to the Montreal National Institute template. Confounding effects of global volume activity and magnetic noise were removed using linear regression and cosine functions (up to a maximum of 1 cycle per 40 scans). Removing the latter confounds corresponds to high-pass filtering of the time series to remove low-frequency artifacts that can arise due to aliased cardiac and other cyclical components. After normalization, three-dimensional spatial smoothing was applied to each volume using a Gaussian kernel of $8 \times 8 \times 8$ mm. Alternating periods of baseline and activation were modeled using a simple delayed box-car reference vector to account for delayed cerebral blood flow after stimulus presentation. Significantly activated pixels were searched for using the General Linear Model approach for time-series data.

To create the subtraction activation image between saccade and antisaccade, data was analyzed using random-effect analysis. Statistical significance was set at the level of $P < 0.001$, uncorrected for multiple comparisons.

Intra-individual comparisons between saccade and antisaccade were analyzed using paired *t*-tests, and statistical significance was set at the level of $P < 0.005$, uncorrected for multiple comparisons.

RESULTS

Behavioral data

Demographic and performance data are summarized in Table 1. The analysis of EOG revealed no differences in prosaccades between the patients and normal controls. In contrast, error rates in antisaccades were higher and latencies of prosaccades and antisaccades were longer in the patient group than in the control group.

fMRI data

Activated areas in the normal control group are shown in Fig. 1a for the saccade tasks and in Fig. 1b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade tasks, regional activations were observed bilaterally in the frontal eye fields (FEF), supplementary eye fields (SEF), and parietal eye fields (PEF), left lenticular

Table 1. Subjects and eye movement performance

	Patients with Schizophrenia	Control
Number of cases (male/female)	18 (12/6)	18 (9/9)
Age (year)	34.8 ± 7.9	37.6 ± 4.8
Education (year)*	11.2 ± 2.9	15.3 ± 2.2
Age at the onset (year)	25.8 ± 6.4	–
HPD equivalence (mg)	16.0 ± 16.1	–
BPRS total score	41.9 ± 7.9	–
Saccade error (%)*	0.5 ± 0.67	0.00 ± 0.00
Saccade latency (ms)*	212.2 ± 30.1	174.2 ± 11.8
Anti-saccade error (%)*	1.1 ± 1.6	0.14 ± 0.35
Anti-saccade latency (ms)*	244.9 ± 48.4	205.6 ± 18.5

Statistical analysis (T-test) *$P < 0.05$.
BPRS, Brief Psychiatric Rating Scale; HPD, haloperidol.

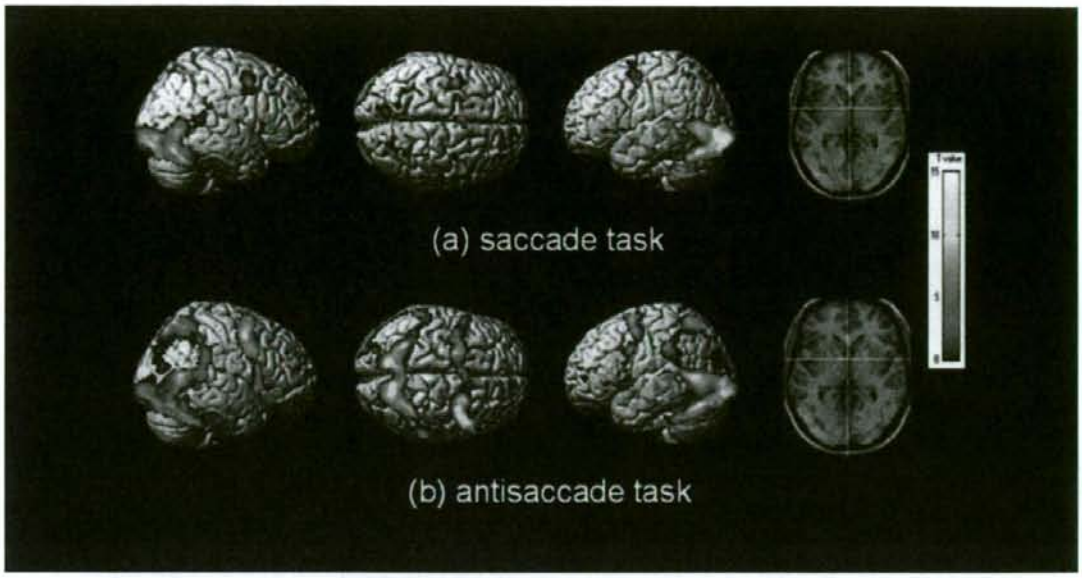

Figure 1. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control condition in healthy subjects. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

nucleus, and bilateral occipital cortices (V1). During the antisaccade tasks, activations were observed in the same regions as during saccade tasks, as well as bilaterally in the inferior parietal lobules (IPL), thalami, right lenticular nucleus, inferior frontal gyrus (IFG), and left dorsolateral prefrontal cortex (DLPFC) (Table 2).

Activation areas in the patient group are shown in Fig. 2a for the saccade tasks and in Fig. 2b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade task, regional activation was observed bilaterally in the FEF, SEF, and PEF, left lenticular nucleus, and V1. These regions are the same as those seen in the normal subject group. However, the patient group also showed activations in the IFG, DLPFC, IPL, lenticular nucleus and thalamus during saccade tasks. During the antisaccade tasks, activation was observed in the same regions as in the saccade tasks (Table 3).

Furthermore, in the normal control group, comparing brain activity during the antisaccade task with that during the saccade task revealed that antisaccade eye movements induced elevated activities in the bilateral FEF, PEF, IPL, ACC, IFG, and DLPFC ($P < 0.005$, uncorrected for multiple comparisons). In the patient group, however, only bilateral activation in the PEF was observed.

Correlation between fMRI activation and eye movement performance

In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. Figure 3 shows the correlation between fMRI activation and eye movement performance in patients with schizophrenia. fMRI activation is calculated from each peak voxel. No significant correlation was observed between two parameters.

DISCUSSION

Our understanding of human cortical control of saccades is derived from observations of cerebral lesions[14–16] and from transcranial magnetic stimulation,[17,18] positron emission tomography,[19,20] and fMRI.[21–24] Previous studies in these areas have indicated that saccadic eye movements are controlled by

Table 2. Brain regions more active during visually guided saccades and antisaccades than during control tasks in healthy subject

Brain region		Saccade vs rest Coordinate				Antisaccade vs rest Coordinate			
		X	*Y*	*Z*	*t*-value	*X*	*Y*	*Z*	*t*-value
DLPFC	R	–	–	–	NS	*50*	*40*	*−8*	4.01
	L	–	–	–	NS	*−44*	*50*	*4*	4.24
FEF	R	*46*	*6*	*50*	5.34	*40*	*−2*	*50*	5.87
	L	*−40*	*−6*	*50*	6.08	*−38*	*−4*	*52*	6.52
SEF	R	*6*	*6*	*62*	4.20	*8*	*8*	*52*	4.20
	L	*−4*	*4*	*60*	5.87	*−2*	*10*	*46*	5.56
PEF	R	*32*	*−54*	*48*	3.80	*26*	*−58*	*54*	6.70
	L	*−30*	*−56*	*56*	4.28	*−26*	*−60*	*52*	7.91
IPL	R	–	–	–	NS	*64*	*−36*	*28*	6.14
	L	–	–	–	NS	*−64*	*−40*	*34*	5.75
Thalamus	R	−12	−18	10	3.96	*10*	*−14*	*8*	8.30
	L	−10	−18	−2	6.53	*−10*	*−16*	*8*	6.29

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; NS, not significant; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

a cortical network that includes the PEF, located in the intraparietal sulcus and superior parietal lobule, the FEF, located in the precentral gyrus, and the SEF, located in the upper medial wall of the frontal lobe. Activation has also been observed in the bilateral dorsolateral prefrontal cortices, supramarginal gyri, anterior cingulate cortices, and thalami during antisaccade tasks.[25] In short, in normal subjects no

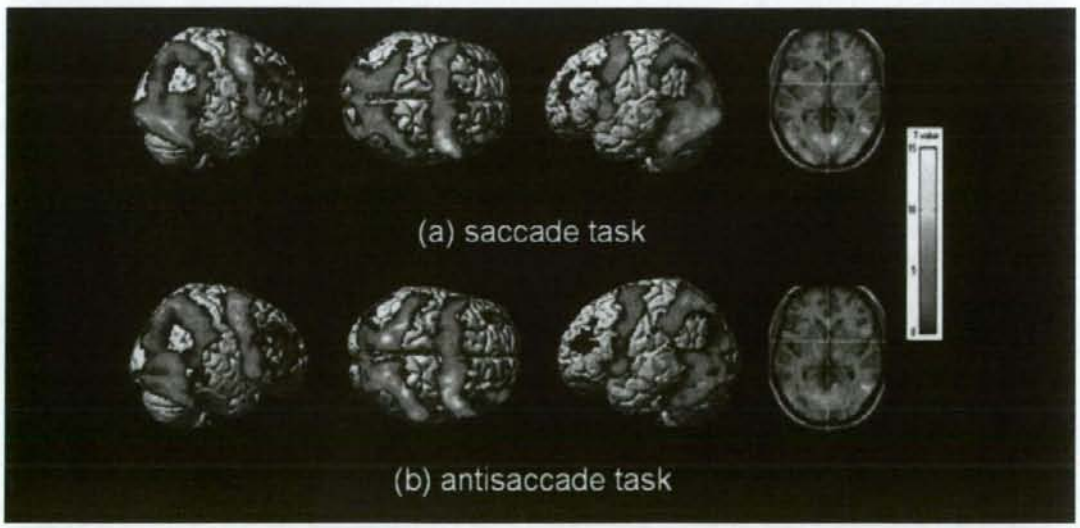

Figure 2. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control conditions in patients with schizophrenia. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

Table 3. Brain regions more active during visually guided saccades and antisaccades than during control tasks in patients with schizophrenia

Brain region		Saccade vs rest Coordinate				Antisaccade vs rest Coordinate			
		X	*Y*	*Z*	*t*-value	*X*	*Y*	*Z*	*t*-value
DLPFC	R	*36*	*56*	*26*	8.80	*42*	*56*	*8*	6.05
	L	*−38*	54	14	4.26	*−36*	*44*	*12*	5.00
FEF	R	*34*	*2*	*64*	8.52	*26*	*0*	*48*	12.06
	L	*−44*	*−4*	*58*	9.91	*−36*	*−6*	*46*	8.99
SEF	R	*12*	*16*	*38*	5.38	*10*	*4*	*48*	5.30
	L	*−8*	*22*	*38*	5.23	*−12*	*0*	*46*	5.53
PEF	R	*30*	*−54*	*48*	7.25	*22*	*−60*	*54*	12.32
	L	*−28*	*−52*	*50*	10.71	*−28*	*−52*	*56*	12.89
IPL	R	56	−32	22	8.63	*62*	*−38*	*18*	5.09
	L	−58	−40	22	3.77	*−62*	*−38*	*18*	4.27
Thalamus	R	12	−14	2	6.70	*10*	*−18*	*−4*	7.09
	L	−12	−14	−2	6.92	*−12*	*−16*	*2*	6.23

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

activation of DLPFC, IFG, striatum, and thalamus were observed during the saccade tasks.

Contrary to previous reports, the present study showed the activations in the DLPFC, IFG, striatum, and thalamus during both the saccade and antisaccade tasks in patients with schizophrenia. In addition, differential activation maps between the antissacade and saccade tasks exhibited the bilateral activation of the FEF, PEF, IPL, ACC, IFG, and DLPFC in normal subjects, whereas only the PEF were activated bilaterally in the patient group. These results show that normal subjects process the saccade and antisaccade tasks in different brain regions, whereas patients with schizophrenia likely use virtually the same regions when processing both tasks. In the patient group, therefore, when brain activations during eye movement tasks were compared directly, the elevated activations of the DLPFC and thalamus normally seen in antisaccade tasks relative to saccade tasks were no longer observed. In comparing the patients to the normal controls, the present study demonstrated higher activity of the thalamus and broad cortical regions (including the prefrontal area), especially during saccade tasks. This suggests hyperactivation, not reduced activation, in the prefrontal cortex and thalamus in patients with schizophrenia. Taken together, though the antisaccade task is cognitively more demanding than the saccade task, these regions in the patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented.

The tasks used in most of the previous studies required subjects to focus on a gazing point, and the reduced activities of the DLPFC and thalamus were observed during the antisaccade tasks in patients with schizophrenia. Three recent studies using fMRI revealed reduced activation in the right DLPFC and reduced activation in the striatum in schizophrenia.[10–12]

In contrast, our results showed higher activities in broad cortical and subcortical regions during the saccade and antisaccade tasks in the patient group as compared with the normal control group. This suggests that these regions could already be activated by the time the schizophrenic patient focuses on the gazing point; therefore, the difference in activation levels between baseline and eye movements becomes smaller in the patient group.

In the present study, we demonstrated the activations in the DLPFC and thalamus during the saccade task in the patient group. The fronto-striato-thalamocortical network,[26–28] including the prefrontal cortex and thalamus, is important for control of antisaccades. Schizophrenia presents with dysfunction in dopaminergic neural networks[29] and the fronto-striato-thalamic circuit.[30,31] Dysfunction in the

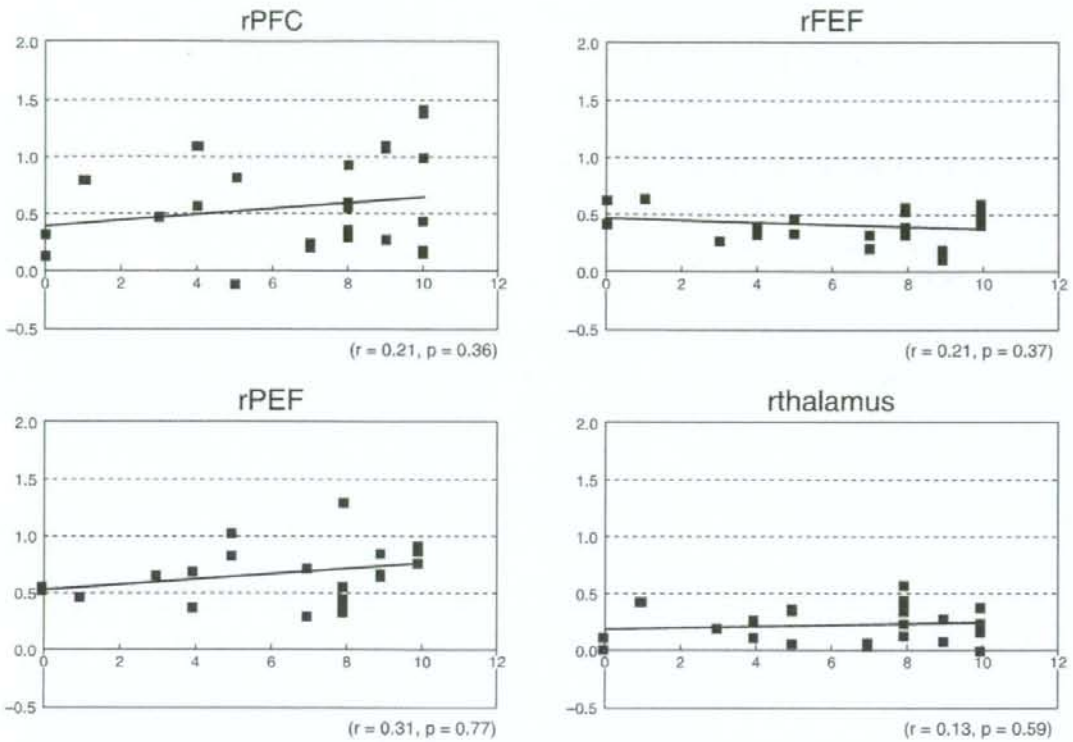

Figure 3. The correlation between brain activation and the number of antisaccade errors. The horizontal axis represents the number of antisaccade errors, and the vertical axis represents the estimated magnetic resonance imaging signal. rFEF, right frontal eye fields; rPEF, right parietal eye fields; rPFC, right prefrontal cortex; rthalamus, right thalamus.

striato-thalamo-cortical dopaminergic circuitry may reduce inhibition of reflexive saccade and thus facilitate saccades for the target direction during the antisaccade task in schizophrenics. Our results indicate that this dysfunction has an important influence on subtle motor control and therefore affects antisaccade generation through both the direct and indirect basal ganglia pathways. These findings suggest that patients with schizophrenia who display antisaccade inhibition errors may present with dysfunction in the fronto-striato-thalamo-cortical network.

Given that previous studies have targeted patients with schizophrenia with poor performance in cognitive tasks, a bias toward reduced brain activations may have been present.[32-36] In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. No significant correlation was observed between the two variables. Therefore, we conclude that the performance did not directly affect the results.

CONCLUSION

In order to examine baseline effect, we employed an eye movement task that did not require subjects to focus on a fixation point during the baseline condition, and compared brain activity between patients with schizophrenia and normal control subjects. In normal subjects, activities in the DLPFC and thalamus were greater during antisaccade tasks than during saccade tasks, whereas no significant difference was observed in patients with schizophrenia. These results suggest that the brains of patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented. Previous studies that used target fixa-

tion at baseline assessment showed reduced activities of the DLPFC and thalamus in patients. In contrast, our study demonstrated hyperactivation of the DLPFC and thalamus in patients, suggesting that in patients with schizophrenia these brain regions were already activated by the time patients viewed a fixed target at baseline. We think that these results reflect the symptom that patients of schizophrenia can not adapt to the environment. Finally, we suspect that patients with schizophrenia may be affected by a defect in the fronto-striato-thalamo-cortical network associated with motor function control.

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REFERENCES

[1] Iacono WG, Tuason VB, Johnson RA. Dissociation of smooth-pursuit and saccadic eye tracking in remitted schizophrenics. An ocular reaction time task that schizophrenic perform well. *Arch. Gen. Psychiatry* 1981; **38**: 991–996.

[2] Levin S, Holzman PS, Rothenberg SJ, Lipton RB. Saccadic eye movements in psychotic patients. *Psychiatry Res.* 1981; **5**: 47–58.

[3] Levin S, Jones A, Stark L, Merrin EL, Holzman PS. Identification of abnormal patterns in eye movements of schizophrenic patients. *Arch. Gen. Psychiatry* 1982; **39**: 1125–1130.

[4] Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol. Psychiatry* 1988; **23**: 670–677.

[5] Everling S, Fischer B. The antisaccade: A review of basic research and clinical studies. *Neuropsychologia* 1998; **36**: 885–899.

[6] Sereno AB, Holzman PS. Antisaccades and smooth pursuit eye movements in schizophrenia. *Biol. Psychiatry* 1995; **37**: 394–401.

[7] McDowell JE, Clementz BA. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: Studies of diagnostic specificity. *Exp. Brain. Res.* 1997; **115**: 333–344.

[8] Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I. Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *J. Psychiatr. Res.* 1990; **24**: 9–24.

[9] Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW. Saccadic eye movements in families multiply affected with schizophrenia: The Maudsley Family Study. *Am. J. Psychiatry* 1998; **155**: 1703–1710.

[10] Raemaekers M, Jansma JM, Cahn W *et al.* Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch. Gen. Psychiatry* 2002; **59**: 313–320.

[11] McDowell JE, Brown GG, Paulus M *et al.* Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol. Psychiatry* 2002; **51**: 216–223.

[12] Tu PC, Yang TH, Kuo WJ, Hsieh JC, Su TP. Neural correlates of antisaccade deficits in schizophrenia, an fMRI study. *J. Psychiatry Res.* 2006; **40**: 606–612.

[13] Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 1971; **9**: 97–113.

[14] Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp. Brain Res.* 1985; **58**: 455–472.

[15] Evdokimidis I, Liakopoulos D, Constantinidis TS, Papageorgiou C. Cortical potentials with antisaccades. *Electroencephalogr. Clin. Neurophysiol.* 1996; **98**: 377–384.

[16] Crevits L, Hanse MC, Tummers P, Van Maele G. Antisaccades and remembered saccades in mild traumatic brain injury. *J. Neurol.* 2000; **247**: 179–182.

[17] Kapoula Z, Isotalo E, Müri RM, Bucci MP, Rivaud-Péchoux S. Effects of transcranial magnetic stimulation of the posterior parietal cortex on saccades and vergence. *Neuroreport* 2001; **12**: 4041–4046.

[18] Leff AP, Scott SK, Rothwell JC, Wise RJ. The planning and guiding of reading saccades: A repetitive transcranial magnetic stimulation study. *Cereb. Cortex.* 2001; **11**: 918–923.

[19] Anderson TJ, Jenkins IH, Brooks DJ, Hawken MB, Frackowiak RS, Kennard C. Cortical control of saccades and fixation in man. A PET study. *Brain* 1994; **117**: 1073–1084.

[20] O'Driscoll GA, Wolff AL, Benkelfat C, Florencio PS, Lal S, Evans AC. Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport* 2000; **11**: 1335–1340.

[21] Gaymard B, Ploner CJ, Rivaud-Péchoux S, Pierrot-Deseilligny C. The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp. Brain Res.* 1999; **129**: 288–301.

[22] Connolly JD, Goodale MA, Desouza JF, Menon RS, Vilis T. A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *J. Neurophysiol.* 2000; **84**: 1645–1655.

[23] Nobre AC, Gitelman DR, Dias EC, Mesulam MM. Covert visual spatial orienting and saccades: Overlapping neural systems. *Neuroimage* 2000; **11**: 210–216.

[24] Matsuo K, Kato C, Sumiyoshi C *et al.* Discrimination of Exner's area and the frontal eye field in humans: Functional magnetic resonance imaging during language and saccade tasks. *Neurosci. Lett.* 2003; **340**: 13–16.
[25] Matsuda T, Matsuura M, Ohkubo T *et al.* Functional MRI mapping of brain activation during visually guided saccades and antisaccades: Cortical and subcortical networks. *Psychiatry Res. Neuroimaging.* 2004; **131**: 147–155.
[26] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 1986; **9**: 357–381.
[27] Petit L, Orssaud C, Tzourio N, Salamon G, Mazoyer B, Berthoz A. PET study of voluntary saccadic eye movements in humans: Basal ganglia-thalamocortical system and cingulate cortex involvement. *J. Neurophysiol.* 1993; **69**: 1009–1017.
[28] McFarland NR, Haber SN. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *J. Neurosci.* 2002; **22**: 8117–8132.
[29] Gerfen CR, Engber TM, Mahan LC *et al.* D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990; **250**: 1429–1432.
[30] Buchsbaum MS, Haier RJ, Potkin SG *et al.* Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. *Arch. Gen. Psychiatry* 1992; **49**: 935–942.
[31] Camchong J, Dyckman KA, Chapman CE, Yanasak NE, McDowell JE. Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol. Psychiatry* 2006; **60**: 235–241.
[32] Frith CD, Friston KJ, Herold S *et al.* Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br. J. Psychiatry* 1995; **167**: 343–349.
[33] Price CJ, Friston KJ. Scanning patients with tasks they can perform. *Hum. Brain Mapp.* 1999; **8**: 102–108.
[34] Bullmore E, Brammer M, Williams SC *et al.* Functional MR imaging of confounded hypofrontality. *Hum. Brain Mapp.* 1999; **8**: 86–91.
[35] Callicott JH, Bertolino A, Mattay VS *et al.* Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb. Cortex.* 2000; **10**: 1078–1092.
[36] Jansma JM, Ramsey NF, Coppola R, Kahn RS. Specific versus nonspecific brain activity in a parametric N-back task. *Neuroimage* 2000; **12**: 688–697.

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Regular Article

Measurement of development of cognitive and attention functions in children using continuous performance test

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Aim: The development of attention function in children is still not sufficiently clear. Although it is difficult to objectively assess attention function, continuous performance tests (CPT) can be used to objectively assess cognitive function along with attention. The development of cognitive and attention functions was examined in children using a CPT.

Methods: A total of 541 healthy girls aged 5–12 years participated. Ten parameters were calculated: numbers of cancellations for either target stimuli (T-cancel) or non-target stimuli (N-cancel), numbers of omission errors (Omission) and commission errors (Commission), hit rate (Hit), false alarm rate (False), mean reaction time for correct response (RT), coefficient of variance for mean reaction time (CVRT), sensitivity index (d'), and lnβ.

Results: The parameters were divided into three types based on pattern of change. T-cancel, False, and Commission, which are related to inhibition of response, N-cancel, Hit, and Omission, which are related to inattention to stimuli, and CVRT, which is related to stability of processing time, exhibited significant change until 5 or 6 years of age. d', which is related to ability to discriminate between target or non-target, exhibited significant change until 8 years of age. RT, which is related to processing time, exhibited significant change until 11 years of age. lnβ exhibited no significant differences among age groups.

Conclusions: These findings indicate that inhibition function, inattention to stimuli, and stability of processing time develop first. Discrimination ability subsequently increases based on these developments, and finally processing time is reduced.

Key words: attention, children, continuous performance test, development.

CONTINUOUS PERFORMANCE TESTS (CPT) require subjects to discriminate between and respond to randomly appearing target and non-target stimuli. A CPT measures attention function using parameters such as hit and false alarm rates and response times. CPT have been used to assess sustained attention in patients with brain injuries,[1] and recently they have also been used to assess the development of attention function.

Various types of CPT have been developed. In a CPT-X task several stimuli are presented randomly, and subjects are required to push a button as quickly as possible only on presentation of the target stimulus. In a CPT-AX task the subjects are required to push a button only when the target stimulus is presented after the presentation of a cue stimulus. A CPT-notX

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task requires that subjects not push a button when the target stimulus is presented. In degraded CPT the stimulus is covered by a pattern of mosaic dots making the image indistinct.

The CPT are also used in clinical studies. Previous studies have shown that patients with epilepsy,[2] brain tumor,[1,3] schizophrenia,[4–7] attention-deficit–hyperactivity disorder (ADHD),[8–13] anxiety disorder,[14] and dementia[15] have attention function deficits.

Several studies have examined the development of attention function in healthy children. Lin *et al.* examined the relationships of age and sex with CPT performance in 341 schoolchildren aged 6–15 years using degraded CPT and CPT-AX.[16] They found that CPT performance parameters (hit rate, false alarm rate, and sensitivity index [d']) exhibited quadratic relationships with age. Sex was associated with hit rate and sensitivity only in testing with degraded CPT. These authors also showed that sustained attention develops during primary school age. Greenberg and Waldman used TOVA (a task similar to CPT-X) in 775 subjects aged 6–16 years to obtain normative developmental data, and found that attention and impulse control develop in a non-linear fashion, first rapidly during early childhood, with a subsequent leveling off during later childhood and adolescence.[17] Conners *et al.* examined normative data for 816 children aged 9–17 years using CPT-notX, and reported that systematic main effects of improved performance at an older age were found for all variables, including reaction time (RT), RT standard error, omission errors, commission errors, and d'.[18] Significant gender effects included more impulsive errors, less variability, and faster RT for boys, with no interactions between age and gender. Chen *et al.* examined the CPT performance of 115 adolescents (junior high school students; mean age ± SD, 14.0 ± 13.0 years) and 345 adults (mean age, 41.3 ± 13.0 years) using degraded CPT and CPT-AX.[19] Their results showed that older age was associated with decreasing hit rate and sensitivity (d'). Men had a higher hit rate and d' than women on degraded CPT.

Further, a recent study combined use of the electroencephalogram (EEG) and CPT in an examination of children aged 9–11 years[20] and normal adults.[21] Studies involving the use of event-related potentials (ERP) and CPT in children aged 12–17 years[22] have also been reported.

The goal of the present study was to measure the development of cognitive and attention functions in children on CPT. CPT can be used to objectively assess cognitive function along with attention. In developmental studies it is necessary to assign the same task to sufficiently large numbers of children over a wide age range. Because the most useful task is one that can be performed by young children, CPT-X was chosen as a comparatively easy one to perform. In addition, it has been reported that CPT can objectively assess abnormalities related to attention function in children with ADHD.[23,24] We believe that normalized CPT data will be helpful in evaluating ADHD and other attention-related disorders.

METHODS

Subjects

This study involved 541 healthy Japanese girls. Individuals with a history of psychiatric disorder were excluded from the study. The study procedure was orally explained to the children and their parents, and informed consent was obtained from the parents. In the present study we assessed data for girls alone in order to exclude effects of sex. The CPT data for children who completed the entire task were used for statistical analysis. Data with a total error >2SD were excluded (numbers of excluded subjects: 5 years, $n = 1$; 6 years, $n = 1$; 7 years, $n = 4$; 8 years, $n = 4$; 9 years, $n = 3$; 10 years, $n = 5$; 11 years, $n = 3$; 12 years, $n = 2$). Finally, the data of 518 subjects aged 5–12 years (numbers of subjects: 5 years, $n = 35$; 6 years, $n = 42$; 7 years, $n = 78$; 8 years, $n = 82$; 9 years, $n = 86$; 10 years, $n = 88$; 11 years, $n = 80$; 12 years, $n = 27$) were analyzed. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tamagawa University.

Procedure

The stimuli of the CPT-X task were visually presented on a cathode-ray tube (CRT) screen controlled by a Windows PC loaded with original software (Continuous Performance Test for Windows Ver.2; Tokyo Medical Dental University, Tokyo, Japan). The stimuli appeared 400 times in a circle approximately 7 cm in diameter and situated at the center of a monitor at a distance of 50 cm from the subject. The visual stimuli in CPT included numerals from 1 to 9. The subject was required to push a button quickly when the target, defined as the number 7, appeared.