Behavioral/Systems/Cognitive

Differential Contributions of Prefrontal and Hippocampal Dopamine D_1 and D_2 Receptors in Human Cognitive Functions

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Dopamine D_1 receptors in the prefrontal cortex (PFC) are important for prefrontal functions, and it is suggested that stimulation of prefrontal D_1 receptors induces an inverted U-shaped response, such that too little or too much D_1 receptor stimulation impairs prefrontal functions. Less is known of the role of D_2 receptors in cognition, but previous studies showed that D_2 receptors in the hippocampus (HPC) might play some roles via HPC–PFC interactions. We measured both D_1 and D_2 receptors in PFC and HPC using positron emission tomography in healthy subjects, with the aim of elucidating how regional D_1 and D_2 receptors are differentially involved in frontal lobe functions and memory. We found an inverted U-shaped relation between prefrontal D_1 receptor binding and Wisconsin Card Sorting Test performance. However, prefrontal D_2 binding has no relation with any neuropsychological measures. Hippocampal D_2 receptor binding showed positive linear correlations not only with memory function but also with frontal lobe functions, but hippocampal D_1 receptor binding had no association with any memory and prefrontal 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 orchestration of prefrontal D_1 receptors and hippocampal D_2 receptors might be necessary for human executive function including working memory.

Key words: dopamine; D_1 receptors; D_2 receptors; prefrontal cortex; hippocampus; positron emission tomography

Introduction

Because dopamine D_1 receptors in the prefrontal cortex (PFC) are several times more abundant than D_2 receptors (Hall et al., 1994), the relationship between D_1 receptors and PFC functions have been widely investigated. Sawaguchi and Goldman-Rakic (1994) demonstrated that local administration of D_1 receptor antagonists into PFC induced impairment in working memory task in nonhuman primate. In human, Müller et al. (1998) reported that systemic administration of a mixed D_1/D_2 agonist facilitated working memory, whereas the selective D_2 agonist had no effect, indicating that the dopaminergic modulation of working memory processes is mediated primarily via D_1 receptors. The use of positron emission tomography (PET) allows us to quantify dopamine receptors *in vivo*, and previous studies reported that altered prefrontal D_1 receptors in schizophrenia were associated with working memory deficits (Okubo et al., 1997; Abi-Dargham et al., 2002).

In contrast to D_1 receptors, relatively less attention has been paid to the role of prefrontal D_2 receptors in cognitive functions. It was reported that blockade of D_2 receptors in PFC did not impair working memory in nonhuman primate (Sawaguchi and Goldman-Rakic, 1994), but some human studies reported that systemic administration of D_2 agonist or antagonist modulated cognitive functions that are subserved by the prefrontal cortex (McDowell et al., 1998; Mehta et al., 1999). Because the density of D_2 receptors in extrastriatal regions is very low (Suhara et al., 1999), PET studies investigating the involvement of extrastriatal D_2 receptors in cognition have been limited. With the introduction of high-affinity PET radioligands such as [^{11}C]FLB457, it has become possible to quantify extrastriatal D_2 receptors by PET (Halldin et al., 1995). Using [^{11}C]FLB457, Kemppainen et al. (2003) reported that a reduction of D_2 receptors in the hippocampus (HPC) in Alzheimer's disease patients was correlated with memory impairments. Our recent PET study also showed that D_2 receptors in HPC were associated not only with memory function but also with frontal lobe functions (Takahashi et al., 2007), suggesting dopaminergic modulation on HPC–PFC inter-

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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 ($p > 0.01$).

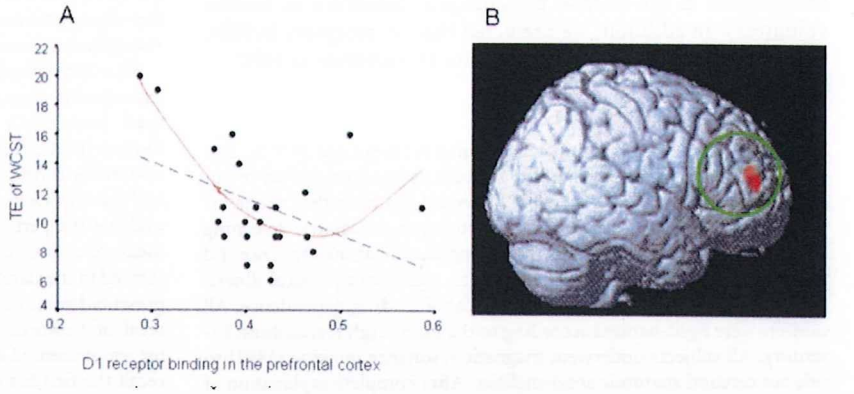

Figure 1. Quadratic (inverted U-shaped) relation between D_1 receptor binding in PFC and performance of WCST. ***A***, ROI analysis revealed a significant quadratic regression between the BP_{ND} value of [^{11}C]SCH23390 in PFC ($BP_{D1\ PFC}$) and TE of WCST. Red solid line, quadratic regression; black 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).

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.

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

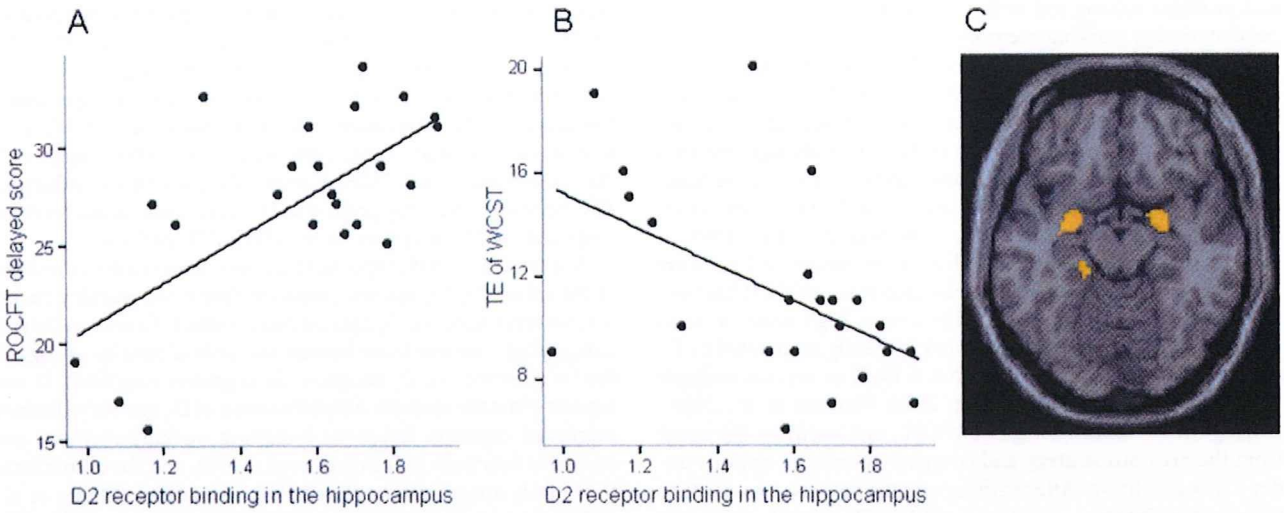

Figure 2. Correlations between D_2 receptor binding in the hippocampus and memory. ***A***, ***B***, Significant positive linear correlations between the BP_{ND} value of [^{11}C]FLB457 in the hippocampus and the delayed recall score of ROCFT and (***B***) TE of WCST revealed by ROI analysis. ***C***, 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.

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Brain Activations during Judgments of Positive Self-conscious Emotion and Positive Basic Emotion: Pride and Joy

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We aimed to investigate the neural correlates associated with judgments of a positive self-conscious emotion, pride, and elucidate the difference between pride and a basic positive emotion, joy, at the neural basis level using functional magnetic resonance imaging. Study of the neural basis associated with pride might contribute to a better understanding of the pride-related behaviors observed in neuropsychiatric disorders. Sixteen healthy volunteers were studied. The participants read sentences expressing joy or pride contents during the scans. Pride conditions activated the right posterior superior temporal sulcus and left temporal pole, the regions implicated in the neural substrate of social cognition or theory of mind. However, against our prediction, we did not find brain activation in the medial prefrontal cortex, a region responsible for inferring others' intention or self-reflection. Joy condition produced activations in the ventral striatum and insula/operculum, the key nodes of processing of hedonic or appetitive stimuli. Our results support the idea that pride is a self-conscious emotion, requiring the ability to detect the intention of others. At the same time, judgment of pride might require less self-reflection compared with those of negative self-conscious emotions such as guilt or embarrassment.

Keywords: medial prefrontal cortex, positive emotions, pride, superior temporal sulcus, theory of mind, ventral striatum

Introduction

Although there have been numerous neuroimaging studies on basic emotions (fear, disgust, happiness, and sadness) that have led to a better understanding of the neuroanatomical correlates of emotions (Lane et al. 1997; Phan et al. 2002), only a few studies on complex social emotions such as guilt, embarrassment, and jealousy have been reported (Shin et al. 2000; Berthoz et al. 2002; Takahashi et al. 2004, 2006).

We previously examined brain activation associated with negative self-conscious emotions, guilt, and embarrassment (Takahashi et al. 2004). Self-conscious emotions are founded in social relationship and arise from concerns about others' evaluations of self (Eisenberg 2000; Tangney and Dearing 2002; Haidt 2003; Kalat and Shiota 2006). In other words, one needs the ability to represent the mental states of others, that is, theory of mind (ToM), to recognize self-conscious emotions. Negative evaluation of self or the behavior of self is fundamental to guilt and embarrassment, whereas positive evaluation of self leads to the emotion of pride. Negative self-conscious emotions promote moral behavior and interpersonal etiquette (Eisenberg 2000; Haidt 2003). Impairment of processing these emotions could lead to amoral, socially inappropriate behaviors observed in neuropsychiatric disorders (Beer et al. 2003; Miller et al. 2003; Sturm et al. 2006).

Supporting the notion that self-conscious emotions involve inferences about others' evaluation of self (Leary 2007), judgment of guilt and embarrassment produced activations in the medial prefrontal cortex (MPFC), posterior superior temporal sulcus (pSTS), and temporal poles (Takahashi et al. 2004; Kalat and Shiota 2006), the regions implicated in ToM, social cognition (Adolphs 2001; Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003), and moral judgment (Greene and Haidt 2002; Moll et al. 2005).

In contrast, a positive self-conscious emotion, pride has been largely unstudied by researchers. Pride refers to self-esteem, joy, or pleasure derived from achievements. It arises when people believe that they are responsible for desired outcomes (Leary 2007). As a self-conscious emotion, pride also drives people to behave in moral, socially appropriate ways (Tracy and Robins 2004a). Specifically, the "achievement-oriented" form of pride promotes prosocial behaviors, such as caregiving and achievement (Tracy and Robins 2004b). However, the hubristic form of pride could be maladaptive, and impairment of processing pride could be related to some psychiatric disorders. Narcissistic personality disorder is characterized by a grandiose sense of self-importance and lack of empathy (American Psychiatric Association 1994). It was reported that empathy and ToM rely on common networks, the MPFC, pSTS, and temporal poles (Vollm et al. 2006). Therefore, the hubristic form of pride could be regarded as a dysfunction of ToM. Affective disorder could also be linked to impairment of the processing of pride. Manic state is a condition with inflated self-esteem, whereas depressive episode could be a condition with low self-esteem (American Psychiatric Association 1994). Studying the neural substrates associated with pride should add to the understanding of the neural basis of these neuropsychiatric disorders.

We aimed to measure brain activations associated with the judgment of pride by showing scenarios, comparing them with brain activations associated with the primary positive emotion, joy, using functional magnetic resonance imaging (fMRI). We hypothesized that joy and pride conditions would show different brain activation patterns, and specifically, that joy condition would activate brain regions involved in hedonic processing, for example, the ventral striatum (Mobbs et al. 2003, 2005; Britton et al. 2006), whereas pride condition would activate the brain regions involved in social cognition (Adolphs 2001) or ToM (Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003), for example, MPFC, pSTS, and temporal poles.

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Materials and Methods

Participants

Sixteen healthy right-handed Japanese university students (8 men, mean age 21.5 years, standard deviation [SD] = 2.2; 8 women, mean age 21.3 years, SD = 1.3) were studied. Their mean educational achievement level was 14.4 years (SD = 1.3). They did not meet any criteria for psychiatric disorders. None of the controls were taking alcohol or medication 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 underwent an 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 Committee.

Materials

Three types of short sentences were provided (neutral, joy, and pride). Each sentence was written in Japanese and in the first person, past tense. Each sentence was expected to express joy, pride, or no prominent emotional content. We used joyful scenarios depicting hedonic, appetitive, and survival events like eating, reproduction, and economic behaviors because these stimuli are thought to be directly related to "basic" positive emotional processing. For most of the pride sentences, we used scenarios in which the protagonist was a winner of a prize or competition as a result of achievement. In order to validate our expected results, we conducted an initial survey. Other university students (20 men and 20 women, mean age 22.5 years, SD = 3.3) than the subjects participating in this fMRI study were screened. We prepared 28–32 sentences for each of 3 conditions (neutral, joy, and pride). The described situations were rated according to how joyful or proud they were using a 7-point analog scale (0 = none, 6 = extremely intense). Based on the initial survey, we selected 18 sentences for each of the 3 conditions. The selected joy sentences were judged to express joy. The mean rating of joy was 4.3 (SD = 0.5). The selected pride sentences were judged to express pride. The mean rating of pride was 4.5 (SD = 0.3). The neutral sentences were judged to express virtually no joy or pride. The mean ratings of joy and pride for neutral sentences were 0.7 (SD = 0.3) and 0.4 (SD = 0.2), respectively. Examples of the sentences are shown in Table 1. The sentences were projected via a computer and a telephoto lens onto a screen mounted on a head coil. The subjects were instructed to read the sentences silently and were told to imagine that the scenario protagonist was himself/herself. They were also told that they should rate the sentences according to how joyful or pride instilling the situations were. After reading each sentence, the subjects were instructed to press a selection button with the right index finger, indicating that they had read and understood it. The experimental design consisted of 6 blocks for each of the 3 conditions (neutral, joy, and pride) interleaved with 20-s rest periods. The order of presentation for the 3 conditions was randomized. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In each 24-s block, 3 different sentences of the same emotional class were presented for 8 s each. After the scan, the subjects read the sentences presented during the scan, and they were asked to rate the sentences according to how they would feel if the scenario protagonist were himself/herself. The participants rated the intensity of joy, pride, and other emotions (anger, sadness, fear, disgust, and shame) for each sentence using a 7-point analog scale.

Table 1
Examples of sentences

Neutral	I took a class at the college.
	I had breakfast.
	I watched the Olympics on TV.
	I recorded a baseball game on video tape.
	I prepared for an examination.
	I went to school yesterday.
	I watched sports news on TV.
	I bought a medicine for cold.
Joy	I won a lottery.
	I won at gambling at a casino.
	I ate my favorite cake.
	I had a date with my girl/boy friend.
	I had a delicious dinner.
	I received a Christmas present.
	I went to Hawaii with my friends.
	I was gifted with a bouquet on my birthday.
Pride	I was awarded a prize for my novel.
	I won the championship in a golf tournament.
	I got a perfect score in mathematics.
	I graduated at the head of my class.
	I won the first prize in a piano contest.
	I graduated from the most prestigious university.
	I obtained a scholarship.
	I won a prize at a scientific meeting.

Images Acquisition

Images were acquired with a 1.5-Tesla Signa system (General Electric, Milwaukee, WI). Functional images of 203 volumes were acquired with T_2^*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; time echo [TE], 50 ms; time repetition [TR], 4 s; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T_1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-dimensional [3D] spoiled Grass sequence, slice thickness 1.5 mm, TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with statistical parametric mapping software package (SPM02) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute template. After normalization, all scans had a resolution of 2 × 2 × 2 mm^3. Functional images were spatially smoothed with a 3D isotropic Gaussian kernel (full width at half maximum of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cutoff period = 192 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of the *t*-statistic were calculated on a voxel-by-voxel basis.

To assess the specific condition effect, we used the contrasts of joy minus neutral (J–N), pride minus neutral (P–N), and pride minus joy (P–J). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. The contrast images were obtained from single-subject analysis and entered into the group analysis. A one-sample *t*-test was applied to determine group activation for each effect. To assess common activation in P–N and J–N conditions, we conducted a conjunction analysis of P–N and J–N contrasts at the second level. A statistical threshold of $P < 0.05$ corrected for multiple comparisons across the whole-brain was used, except for a priori hypothesized regions, which were thresholded at $P < 0.0005$ uncorrected (only clusters involving 10 or more contiguous voxels are reported). These a priori regions of interest included the ToM-related regions (MPFC, pSTS, and temporal poles), reward/food-related regions (striatum, insula, and orbitofrontal cortex), and emotion-related limbic regions (amygdalohippocampal regions and anterior cingulate cortex). We conducted regression analyses to demonstrate a more direct link between regional brain activities with the subjective judgments of joy and pride. Using the mean of the ratings of joy and pride for each subject as the covariate, regression analyses with the contrasts (J–N and P–N) and the covariate were done at the second level (height threshold at $P < 0.001$, uncorrected, and extent threshold of 5 voxels). The masks of J–N and P–N contrasts from one-sample *t*-test ($P < 0.001$) were applied to confine the regions where significant activations were observed. Using

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the effect sizes, representing the percent signal changes, of the contrasts (J-N and P-N) at the peak coordinates uncovered in the regression analyses, we plotted the fMRI signal changes and ratings of joy and pride.

Results

Self-rating

The neutral sentences were judged as carrying no prominent emotions. The mean ratings of joy and pride for neutral sentences were, respectively, 0.7 (SD = 0.7) and 0.4 (SD = 0.4), for joy sentences 4.9 (SD = 0.7) and 1.1 (SD = 1.1), and for pride 4.1 (SD = 0.9) and 4.9 (SD = 0.6). Ratings of other emotions (anger, sadness, fear, disgust, and shame) were virtually zero. Although pride sentences were judged as containing joy, their mean ratings of pride were significantly greater than those of joy (t = 2.9, degrees of freedom [df] = 30, P = 0.007). The mean ratings of joy were significantly greater for joy sentences than for pride sentences (t = 2.9, df = 30, P = 0.007).

fMRI Result

Pride condition relative to neutral condition (P-N) produced greater activations in the right pSTS, left temporal pole (Table 2 and Fig. 1*A*). We did not find significant activation in the MPFC. Joy condition relative to neutral condition (J-N) produced greater activations in the ventral striatum including the nucleus accumbens, anterior cingulate cortex, hippocampal regions, and insula/operculum (Table 2 and Fig. 1*B*). P-J condition produced greater activations in the right pSTS (x = 42, y = -66, z = 22; t = 7.39; 92 voxels). A conjunction analysis of P-N and J-N contrasts revealed no significant activations.

Regression analyses revealed positive linear correlations between the self-rating of pride and the degree of activation in the pSTS (middle temporal gyrus, x = 44, y = -66, z = 20; t = 5.25; 14 voxels) (Figs 2*A* and 3*A*). There were positive linear correlations between the self-rating of joy and the degree of activation in the ventral striatum (nucleus accumbens, x = -12, y = 2, z = -6; t = 6.26; 6 voxels) (Figs 2*B* and 3*B*).

Discussion

This study demonstrated that the brain activations during judgments of the positive self-conscious emotion, pride, showed different patterns from those of the basic positive emotion, joy. Pride conditions relative to neutral condition produced greater activity in the right pSTS and left temporal pole, the components of neural substrates of social cognition or ToM (Allison et al. 2000; Adolphs 2001; Frith U and Frith CD 2003; Gallagher and Frith 2003; Moll et al. 2005). In contrast, joy conditions relative to neutral condition produced greater activity in the key nodes of processing hedonic and appetitive stimuli, the ventral striatum including the nucleus accumbens (Breiter and Rosen 1999; Salamone et al. 2003; Cardinal and Everitt 2004) and insula/operculum (Britton et al. 2006; Porubska et al. 2006; Rolls 2006). In addition, regression analyses showed that the subjective ratings of pride and joy correlated with the degrees of activation in the pSTS and ventral striatum, respectively.

Pride, by definition, is subsumed by basic emotion, joy (Tracy and Robins 2004a). In fact, our behavioral rating results showed that ratings of joy for pride sentences were high, although they were lower for pride sentences than for joy sentences. Therefore, it was expected that activations in the regions related to basic emotions, for example, the ventral striatum, might be observed. However, significant activation in such regions was not found, and the conjunction analysis of P-N and J-N did not find common activation in these regions, suggesting that joy derived from pride scenarios was not high enough to activate these regions. We used joyful scenarios containing hedonic and appetitive events that usually motivate biological behaviors like eating, reproduction, and economic behaviors. The mesolimbic dopamine system from the ventral tegmental area to the nucleus accumbens mediates the motivation to obtain reward. In other words, dopamine systems are more necessary for "wanting" incentives than for "liking" them (Berridge and Robinson 1998). Motivational processes are important for positive emotions such as happiness and joy (Lyubomirsky 2001). In an fMRI environment, it is difficult to induce liking, but participants might have felt "wanting" for reward such as money or food, leading to activation in the ventral striatum (Breiter and Rosen 1999; Salamone et al. 2003; Cardinal and Everitt 2004). In contrast, although pride sentences were articulated as joyful, their lack of hedonic contents might account for the lack of activation in such regions.

Table 2
Brain activations in pride condition and joy condition relative to neutral condition

Brain regions	L/R	Coordinates			t-score
		x	y	z	
Pride-neutral					
pSTS	R	42	−66	20	4.30
Temporal poles	L	−50	20	−24	4.62
Joy-neutral					
Ventral striatum	R	4	4	−6	4.5
Anterior cingulate cortex	L	−6	38	12	4.6
Hippocampal regions	L/R	−32	−16	−18	4.94
Insula/operculum	L/R	40	−28	18	5.39

Note: L, left; R, right. Coordinates and t-score refer to the peak of each brain region.

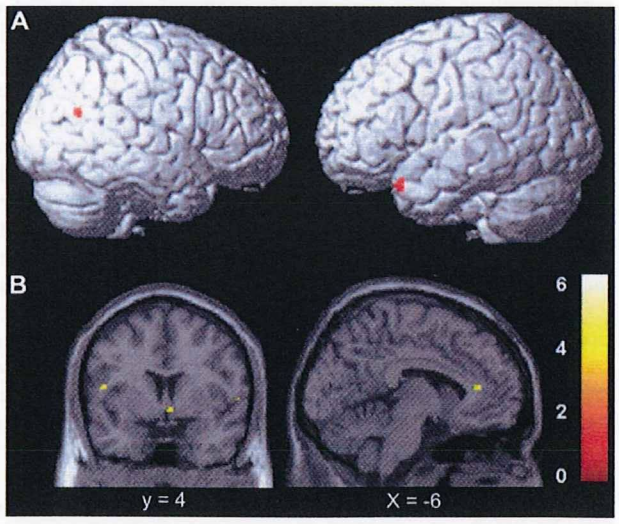

Figure 1. Images showing brain activation in joy and pride conditions relative to neutral condition. (*A*) Pride minus neutral. Activated regions were in the right posterior STS and left temporal pole. (*B*) Joy minus neutral. Activations in the ventral striatum, insula/operculum, and anterior cingulate were shown. Significant differences were recognized at a height threshold (t > 4.07; P < 0.0005, uncorrected) and extent threshold (10 voxels).

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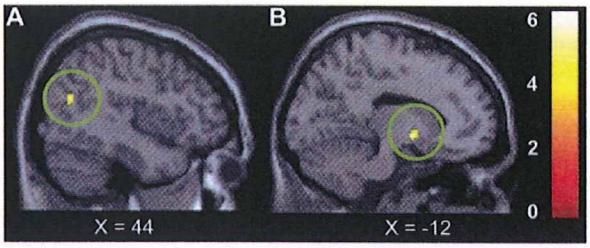

Figure 2. Correlation between brain activation and the self-ratings of pride and joy, with height threshold ($P < 0.001$) and extent threshold (5 voxels). (*A*) There was positive linear correlations between self-rating of pride and the degree of activation in the pSTS. (*B*) There was positive linear correlations between self-rating of joy and the degree of activation in the ventral striatum. The bar shows the range of the *t*-score. Within the image, L indicates left. Numbers in the bottom low indicate the *z*-coordinates of the Montreal Neurological Institute brain.

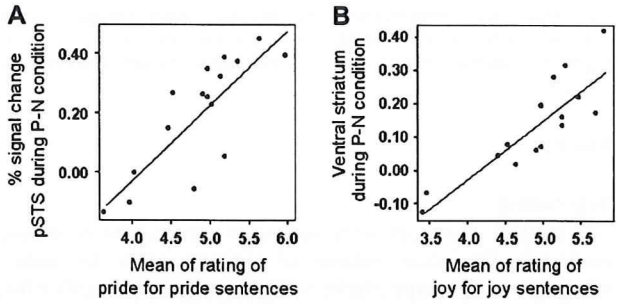

Figure 3. Plots and regression lines of correlations between self-ratings and the degree of activation in the brain regions. (*A*) Positive correlations ($r = 0.81$, df = 14, $P < 0.001$) between self-rating of pride and the degree of activation in the pSTS. (*B*) Positive linear correlations ($r = 0.86$, df = 14, $P < 0.001$) between self-rating of joy and the degree of activation in the ventral striatum.

Furthermore, as discussed below, unfamiliarity with some events depicted in pride scenarios might attenuate wanting for such events.

Our previous study has shown activation in the 3 key regions of ToM, the MPFC, pSTS, and temporal poles (Frith U and Frith CD 2003; Gallagher and Frith 2003) during the evaluative process of negative self-conscious emotions such as guilt and embarrassment (Takahashi et al. 2004). In addition, a recent clinical study reported that patients with frontotemporal lobar degeneration had impaired processing of negative self-conscious emotions (Sturm et al. 2006). Therefore, we expected that a positive self-conscious emotion would also recruit these regions. Although activations in the pSTS and temporal poles by pride scenarios were in agreement with our prediction, in disagreement was the lack of significant activation in the MPFC.

Although the precise roles of these 3 regions remain unclear, it was suggested that the pSTS and temporal poles are more concerned with the nature of socially relevant stimuli (Gallagher and Frith 2003; Decety and Grezes 2006). In other words, these regions are involved mainly in the early stage of social cognition, initial appraisal of socially relevant stimuli that support ToM ability, but not in ToM reasoning per se (Frith U and Frith CD 2003; Gallagher and Frith 2003).

Originally, the STS was known to be activated by biological motions such as movement of eyes, mouth, hands, and body (Allison et al. 2000), and it has been suggested to have a more general function in social cognition such as detecting explicit behavioral information that signals the intention of others (Gallagher and Frith 2003) and behavior of agents (Frith U and Frith CD 2003). The higher order association cortices including the pSTS mature in the last stage of brain development (Gogtay et al. 2004), and this might be associated with the fact that, like all self-conscious emotions, pride emerges later in the course of development than basic emotions like fear and joy (Tracy and Robins 2007). In addition, impairments in recognizing self-conscious emotions have been reported in children with autism (Capps et al. 1992; Kasari et al. 1993), in which STS abnormalities are highly implicated (Zilbovicius et al. 2006).

Bilateral temporal poles with greater effect on the left side have also been consistently recruited during ToM task (Calarge et al. 2003; Frith U and Frith CD 2003; Gallagher and Frith 2003). Although the left temporal pole contributes to the composition of sentence meaning (Vandenberghe et al. 2002), the temporal pole activation in P-N condition cannot simply be attributed to the use of sentences because neutral stimuli also require sentence comprehension. The temporal poles are generally engaged in retrieving episodic memories such as emotional and autobiographical memory (Fink et al. 1996; Dolan et al. 2000; Sugiura et al. 2006). In ToM task, the retrieval of episodic memories enables us to understand and simulate the mental state of others (Gallagher and Frith 2003). This role of memory process in understanding others' mental state might result in activation in the temporal pole in the P-N condition. Additionally, a recent study has suggested that this region is involved in storage and recall of contextual information (Mobbs et al. 2006). Because the subjects might not have direct experience of all the pride scenarios, the activation in the temporal pole may suggest that the subjects were reminded of contextual information of themselves or others (e.g., famous person) associated with pride scenarios (Mobbs et al. 2006; Sugiura et al. 2006).

The MPFC appears to be responsible for ToM reasoning or mentalizing, the ability to represent others' perspective (Frith U and Frith CD 2003; Gallagher and Frith 2003; Amodio and Frith 2006). This ability allows us to infer the cause of others' behavior, attribution. Previous studies have shown activation in the MPFC during judgments made on the basis of attributional information (Amodio and Frith 2006), and it is suggested that the MPFC is activated when cues that have been processed in an early stage of social cognition are used in a particular way, that is, to infer the intention (Gallagher and Frith 2003; Ochsner 2004) and emotional state (Aichhorn et al. 2006) of others. The lack of activation in the MPFC might stem from pride scenarios such as used in the present study. Most pride scenarios described situations in which the protagonist was a winner of a prize or competition as a result of achievement. Winning a prize or competition, by definition, is a symbol that inevitably indicates others' positive evaluations or judgments for one's own achievement. Therefore, in order to detect how one is evaluated by others in these situations, one might have less necessity to "infer" the mental state of others by using cues that have been processed in the early stage of social cognition. Another explanation for the lack of significant activation in the MPFC during judgments of pride might be possible. The argument regarding the role of the MPFC in ToM is mainly based on classical, explicit ToM tasks that usually used false belief stories (Frith U and Frith CD 2003; Gallagher and Frith 2003), whereas our task was an implicit ToM task in which the subjects were not explicitly instructed to represent the mental state of others, and the pSTS rather than MPFC plays a more

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central role (Saxe and Kanwisher 2003). A body of psychological studies has demonstrated that people have self-positivity biases, tendencies to have a positive attitude toward self. People tend to accept responsibility for desired outcomes but to attribute negative events to external causes (Greenwald and Banaji 1995; Leary 2007). Self-positivity biases are known to operate implicitly and automatically without conscious reflection (Greenwald and Banaji 1995; Leary 2007). The MPFC is a key node of a neural system subserving explicit reflection of self (Johnson et al. 2002). Therefore, the subjects might have judged some scenarios as pride ones without elaborate self-reflection.

This study has some limitations. First, as mentioned above, a complex self-conscious emotion could be accompanied by basic emotion. Although we understand that it is not feasible to assess a "pure" form of emotion, the results of regression analysis tell us that brain activations during pride condition could not simply be accounted for by the accompanying emotion. Second, self-conscious emotions depend on society and culture (Haidt 2003). The social background of participants, such as generation, religion, and education, could be confounding factors. For example, there are some empirical studies to support the traditional view that Japanese culture is collectivistic, putting a premium on social harmony, whereas Northern American culture is individualistic, highlighting personal achievement (Kitayama et al. 2006). At the same time, individualism is increasing in contemporary Japanese society especially among the young generation (Cusick 2007). Therefore, examining the effect of generations on self-conscious emotions would be an interesting future theme, and any generalization of our findings needs to be approached with caution. Finally, self-conscious emotions are more difficult to elicit in an MRI environment than basic emotions (Tracy and Robins 2004a). For this reason, we used an emotion judgment task, not an emotion induction task. To complement fMRI studies, lesion studies that can assess real-life human social behavior are recommended.

In conclusion, we investigated the neural substrates of judgments of a positive self-conscious emotion and demonstrated a difference from those of a basic positive emotion at a neural basis level. Supporting the concept that pride could be regarded as a member of the self-conscious emotions family, judgments of pride produced activation in the components of neural substrates implicated in social cognition or ToM. At the same time, judgment of pride might require less self-reflection compared with those of negative self-conscious emotions such as guilt or embarrassment. We expect our findings regarding joy and pride to have broad implications for the neural basis of some neuropsychiatric disorders such as depression or schizophrenia characterized by anhedonia and narcissistic personality or affective disorder, characterized by inappropriate pride, respectively.

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Notes

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Neural Correlates of Human Virtue Judgment

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Neuroimaging studies have demonstrated that the brain regions implicated in moral cognition. However, those studies have focused exclusively on violation of social norms and negative moral emotions, and very little effort has been expended on the investigation of positive reactions to moral excellence. It remains unclear whether the brain regions implicated in moral cognition have specific roles in processing moral violation or, more generally, process human morality per se. Using functional magnetic resonance imaging, brain activations during evaluation of moral beauty and depravity were investigated. Praiseworthiness for moral beauty was associated with activation in the orbitofrontal cortex, whereas blameworthiness for moral depravity was related to the posterior superior temporal sulcus. Humans might have developed different neurocognitive systems for evaluating blameworthiness and praiseworthiness. The central process of moral beauty evaluation might be related to that of aesthetic evaluation. Our finding might contribute to a better understanding of human morality.

Keywords: blameworthiness, moral, orbitofrontal cortex, praiseworthiness, superior temporal sulcus, virtue

Introduction

The emerging field of cognitive neuroscience is providing new insights into the neural basis of moral cognition and behaviors. As David Hume (1978) and Adam Smith (1976) already noted in the 18th century, some contemporary philosophers have emphasized the importance of emotion and intuition in moral judgment, although moral reasoning could contribute to moral judgment (Haidt 2001; Greene and Haidt 2002). Supporting this view, recent neuroimaging studies and brain lesion studies have demonstrated that emotion-related brain regions such as the posterior superior temporal sulcus (pSTS), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), and amygdala play important roles in moral judgment (Damasio 2000; Greene and Haidt 2002; Takahashi et al. 2004; Moll et al. 2005). Previous psychological as well as neuroimaging studies mainly focused on violation of social norms and negative moral emotions such as guilt or embarrassment (Greene and Haidt 2002; Haidt 2003a, 2003b; Takahashi et al. 2004; Moll et al. 2005; Mobbs et al. 2007). Morals are standards or principles of right or wrong behaviors and the goodness or badness of human character. It remains unclear whether the brain regions implicated in moral cognition are specialized in processing immorality, that is, negative deviance from social norms or, more generally, processing deviance from social standards regardless of whether the stimuli positively or negatively deviate from them. There has been very little study on positive moral emotions or psychological responses to moral beauty, but with the advent of the positive psychology movement (Seligman and Csikszentmihalyi 2000), researchers have started to focus on positive moral emotions. Many people experience spontaneous pleasure when they can help others without any expectation of reward. Neuroimaging studies suggest that cooperative behaviors might be psychologically rewarding (Rilling et al. 2002; de Quervain et al. 2004; Moll et al. 2006). It is also human nature that we are easily and strongly moved by people who are cooperating with others. Haidt (2003a, 2003b) started to call an emotion elicited by others' act of virtue or moral beauty as "elevation." When people observe others' virtuous, commendable acts, they feel warm, pleasant, and "tingling" feelings and are motivated to help others and to become better people themselves. Hume (1978) wrote that "a generous and noble character never fails to charm and delight us" and Smith (1976) noted that "man desires, not only praise, but praiseworthiness." We also could have an aesthetic feeling in human virtuous acts and be often attracted by the beauty itself (Haidt 2003a). However, there are very few studies to have concentrated on this aspect of moral beauty. According to Haidt (2003a), we cannot have a full understanding of human morality until we can explain why and how people are so powerfully affected by the sight of a stranger helping another stranger.

For the evolution and persistence of cooperation, it is necessary for humans to detect cheaters and cooperators. Otherwise, selfish strategies will eliminate cooperative strategies (Axelrod and Hamilton 1981; Cosmides and Tooby 1992). Cosmides and Tooby (1992) argued that humans have evolved neurocognitive systems that specialize in detecting "cheating," violation of social contracts, and that produce a feeling that those who violate social norms should be blamed and punished. In fact, functional magnetic resonance imaging (fMRI) studies reported activation in brain regions such as pSTS and MPFC during detection of violation of social contracts (Canessa et al. 2005; Fiddick et al. 2005). On the other hand, it is also argued that humans have evolved a neurocognitive system that skillfully assesses the cooperativeness of others (Price 2006), and empirical evidence suggests that people will cooperate with those whom they have observed cooperating with others (Wedekind and Milinski 2000; Milinski et al. 2002). However, there is as yet no documented study regarding the investigation

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of the neural correlates during the observance of praiseworthy, virtuous acts of others.

In this study, we investigated the brain activation associated with the judgment of moral beauty, virtue, comparing it with that of moral depravity, vice. We hypothesized that the judgment of moral beauty and depravity would show different brain activation patterns. Specifically, moral depravity would be linked to brain regions, such as pSTS and MPFC, and moral beauty would recruit the brain regions implicated in positive emotions, such as OFC.

Materials and Methods

Participants

Fifteen healthy volunteers (mean age 20.1 years, standard deviation [SD] = 0.8) participated in this study. All subjects were Japanese and right-handed. The participants were free of any criteria for neuropsychiatric disorders based on unstructured psychiatric screening interviews. None of the participants were taking 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 participants underwent an MRI to rule out cerebral anatomic abnormalities. After complete explanation of the study, written informed consent was obtained from all participants and the study was approved by the Institutional Ethics Committee.

Materials

Three types of short sentences were provided (neutral, moral beauty, and moral depravity). Each sentence was written in Japanese and in the 3rd person. Sentences of moral depravity were expressing moral violation, and those of moral beauty were expressing acts like charity, self-sacrifice, altruism, humanitarianism, and so on. Neutral sentences were expected to express no prominent emotional content. In order to validate our expected results, we conducted an initial survey. We prepared 30–35 sentences for each of 3 conditions (neutral, moral beauty, and moral depravity). Forty-two other healthy volunteers (21 males and 21 females, mean age 22.5 years, SD = 3.3) than the subjects participating in this fMRI study were screened. Using 7-point Likert scales, they read and rated each sentence in terms of morality/immorality (−3 = extremely immoral, 0 = neither moral nor immoral, and 3 = extremely moral) and praiseworthiness/blameworthiness (−3 = extremely blameworthy, 0 = neither praiseworthy nor blameworthy, and 3 = extremely praiseworthy). Based on the initial survey, we selected 18 sentences for each of the 3 conditions. These sentences are shown in Supplementary Table S1. The sentences were projected via a computer and a telephoto lens onto a screen mounted on a head coil. The subjects were instructed to read the sentences silently and were told to imagine the events described in the sentences. They were also told that they should rate the sentences according to how moral/immoral or praiseworthy/blameworthy the events were. After reading each sentence, the subjects were instructed to press a selection button with the right index finger, indicating that they had read and understood it. The experimental design consisted of 6 blocks for each of the 3 conditions (neutral, moral beauty, and moral depravity) interleaved with 20-s rest periods. We used a block design rather than an event-related design as it is difficult to obtain sufficient understandable stimuli, that is, depictions of moral beauty and depravity are difficult to parse rapidly (Luo et al. 2006). The order of presentation for the 3 conditions was randomized. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In each 24-s block, 3 different sentences of the same condition were presented for 8 s each. Using 7-point Likert scales, the participants rated each sentence in terms of morality/immorality and praiseworthiness/blameworthiness after the scans.

Image Acquisition

Images were acquired with a 1.5 Tesla Signa system (General Electric, Milwaukee, WI). Functional images of 203 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent contrast. Each volume consisted of 40 transaxial contiguous slices with a slice thickness of 3 mm to cover almost the whole brain (flip angle, 90°; time echo [TE], 50 ms; time repetition [TR], 4 s; matrix, 64 × 64; and field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-dimensional Spoiled-Grass sequence, slice thickness 1.5 mm; TE, 9 ms; TR, 22 ms; flip angle, 30°; matrix, 256 × 192; and field of view, 25 × 25 cm).

Analysis of Functional Imaging Data

Data analysis was performed with statistical parametric mapping software package (SPM02) (Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA). All volumes were realigned to the 1st volume of each session to correct for subject motion and were spatially normalized to the standard space defined by the Montreal Neurological Institute template. After normalization, all scans had a resolution of 2 × 2 × 2 mm^3. Functional images were spatially smoothed with a 3-dimensional isotropic Gaussian kernel (full width at half maximum of 8 mm). Low frequency noise was removed by applying a high-pass filter (cutoff period = 192 s) to the fMRI time series at each voxel. A temporal smoothing function was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of the *t*-statistic were calculated on a voxel-by-voxel basis.

To assess the specific condition effect, we used the contrasts of the moral beauty minus neutral (MB − N) and moral depravity minus neutral (MD − N). A random effects model, which estimates the error variance for each condition across the subjects, was implemented for group analysis. This procedure provides a better generalization for the population from which data are obtained. The contrast images were obtained from single-subject analysis and entered into the group analysis. A 1-sample *t*-test was applied to determine group activation for each effect. We used SPM's small volume correction to correct for multiple testing in regions about which we had a priori hypothesis. These a priori volumes of interest (VOIs) included the pSTS, MPFC, and OFC. VOIs for pSTS (angular gyrus), MPFC (superior and medial frontal gyrus), and OFC (inferior frontal gyrus) were defined by standardized VOI templates implemented in brain atlas software (Maldjian et al. 2003). Significant activations surviving this correction at $P < 0.05$ are reported. We describe activations outside regions of interest surviving a threshold of $P < 0.001$, uncorrected, with an extent threshold of 10 contiguous voxels. To assess common activation in MB − N and MD conditions, we conducted a conjunction analysis of MB − N and MD − N contrasts at the 2nd level.

We conducted regression analysis to demonstrate a more direct link between regional brain activities with the subjective judgments of praiseworthiness and blameworthiness. Using the mean of the ratings of praiseworthiness and blameworthiness for each subject as the covariate, regression analysis with the contrasts (MB − N and MD − N) and the covariate was performed at the 2nd level. The masks of MB − N and MD − N contrasts from the 1-sample *t*-test ($P < 0.001$) were applied to confine the regions where significant activations were observed. Using the effect sizes, representing the percent signal change, of the contrasts (MB − N and MD − N) at the peak coordinates uncovered by regression analysis, we plotted the fMRI signal changes and ratings of praiseworthiness and blameworthiness.

Results

Initial Survey

As we predicted, neutral sentences were judged neither moral/praiseworthy nor immoral/blameworthy. The averages of the ratings of morality/immorality and praiseworthiness/blameworthiness for neutral sentences were 0.0 (SD = 0.1) and 0.0 (SD = 0.1), respectively. The average of ratings of morality and

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praiseworthiness for 18 sentences of moral beauty were 2.3 (SD = 0.8) and 1.8 (SD = 0.9), respectively. The average of ratings of immorality and blameworthiness for 18 sentences of moral depravity were -2.4 (SD = 0.7) and -2.1 (SD = 0.8), respectively.

Self-Rating

The self-rating results of the subjects participating in the fMRI study were comparable to the results obtained in the initial survey. The averages of the ratings of morality/immorality and praiseworthiness/blameworthiness for neutral sentences were 0.1 (SD = 0.2) and 0.0 (SD = 0.1), those of morality and praiseworthiness for sentences of moral beauty were 2.5 (SD = 0.3) and 2.1 (SD = 0.5), and those of immorality and blameworthiness for sentences of moral depravity were -2.4 (SD = 0.3) and -2.1 (SD = 0.4), respectively. Self-ratings of immorality were correlated with blameworthiness ($r = 0.58$, $P = 0.025$), and those of morality were correlated with praiseworthiness ($r = 0.68$, $P = 0.005$).

fMRI Result

The MB-N condition produced activations in the left OFC, left dorsal lateral prefrontal cortex (DLPFC), left supplementary motor area (SMA), left temporal pole, and visual cortex, (Table 1 and Fig. 1*A*). The MD - N condition produced activations in the left pSTS and MPFC (Table 1 and Fig. 1*B*). The activations in a priori regions (pSTS, MPFC, and OFC) survived a threshold of $P < 0.05$ corrected for multiple comparisons across a small VOI. A conjunction analysis of MB - N and MD - N contrast revealed no significant activations.

Regression analysis revealed positive linear correlations between self-rating of praiseworthiness and the degree of activation in the left OFC ($x = -38$, $y = 28$, and $z = -20$) in MB - N contrast (Figs 2*A* and 3*A*). There were correlations between self-rating of blameworthiness and the degree of activation in the left pSTS ($x = -54$, $y = -66$, and $z = 28$) in MD - N contrast (Figs 2*B* and 3*B*). Theses correlations in a priori regions (pSTSC and OFC) survived a threshold of $P < 0.05$ corrected for multiple comparisons across a small VOI.

Discussion

This study has demonstrated that the brain activations during evaluation of positive deviance from the moral standard, moral beauty, showed different patterns from those of negative deviance, moral depravity. In line with previous reports, moral depravity conditions relative to neutral condition produced greater activity in the left pSTS and MPFC, the components of neural substrates that have been suggested to be involved in human moral cognition (Takahashi et al. 2004; Moll et al. 2005). A novel finding in this study was that moral beauty conditions relative to neutral condition produced greater activity in the left frontal regions, such as OFC, DLPFC, and SMA. This means that the regions suggested to play important roles in moral cognition are more specialized in processing moral violation and do not cover human morality per se.

Although self-ratings of immorality were correlated with blameworthiness and those of morality were correlated with praiseworthiness, empirical evidence suggests that blameworthiness for immoral acts and praiseworthiness for commendable or cooperative acts were not symmetrical. In other words, blameworthiness for impulsive immoral acts without deliberate intention was discounted compared with deliberate immoral acts, whereas praiseworthiness for commendable acts was not discounted regardless of whether the positive acts were impulsive or deliberate (Pizarro et al. 2003). This is also common in legal culpability. This means that people tend to link blameworthiness to intention and the process of wrongdoing, whereas they tend to link praiseworthiness to outcomes of positive acts regardless of deliberate intention or not.

Table 1
Brain activations in moral beauty condition and moral depravity condition relative to neutral condition

Brain region	L/R	Coordinates			*Z*-score
		x	*y*	*z*	
Moral beauty-neutral					
Visual cortex	L/R	14	−90	−8	4.59
OFC*	L	−40	32	−20	3.39
Temporal pole	L	−50	18	−24	3.51
SMA	L	−48	0	48	3.52
DLPFC	L	−52	26	14	3.30
Moral deprivity-neutral					
MPFC*	L/R	6	58	14	4.35
pSTS*	L	−54	−64	30	3.40

Note: Coordinates and *Z*-score refer to the peak of each brain region. L, left; R, right. All values, $P < 0.001$, uncorrected. *$P < 0.05$, corrected for multiple comparisons across a small VOI.

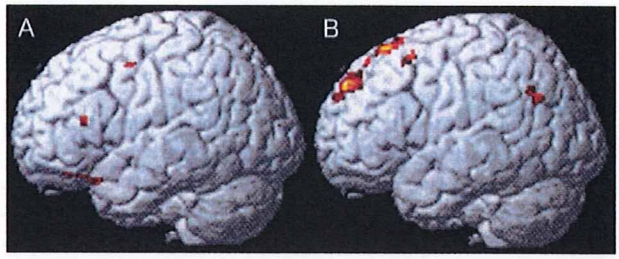

Figure 1. Images showing brain activations in response to (*A*) MB − N condition and (*B*) MD − N condition. (*A*) Significant activation in OFC is shown. (*B*) Significant activations in MPFC and pSTS are shown.

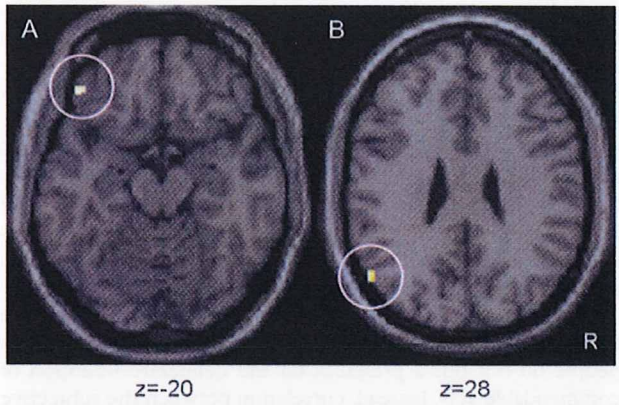

Figure 2. Correlations between self-ratings of (*A*) praiseworthiness (*B*) blameworthiness and brain activations. (*A*) Correlation between self-rating of praiseworthiness and degree of activation in left OFC in MB − N contrast. (*B*) Correlations between self-rating of blameworthiness and degree of activation in pSTS in MD − N contrast. Within the images, R indicates right. Numbers at bottom indicate coordinates of Montreal Neurological Institute brain.

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Figure 3. Regression lines of correlations between (*A*) praiseworthiness (*B*) blameworthiness and degree of brain activation. (*A*) There were correlations ($r = 0.82$, degrees of freedom [df] = 13, $P < 0.001$) between self-rating of praiseworthiness and degree of activation in OFC. (*B*) There were positive linear correlations ($r = -0.83$, df = 13, $P < 0.001$) between self-rating of blameworthiness and degree of activation in pSTS.

Moral depravity produced activation in the pSTS and MPFC, and the degree of pSTS activation was correlated with blameworthiness. Originally, STS was known to be activated by biological motions such as movement of eyes, mouth, hands, and body (Allison et al. 2000), and it has been suggested to have a more general function in social cognition such as detecting behavioral information that signals the intention of others (Gallagher and Frith 2003) and behavior of agents (Frith U and Frith CD 2003). MPFC appears to be responsible for inferring the cause of others' behavior, attribution. Previous studies have shown activation in the MPFC during judgments made on the basis of attributional information (Amodio and Frith 2006). It is suggested that, for the evolution and persistence of cooperation, humans have evolved neurocognitive systems that specialize in the detection of cheating and that motivate people to blame and punish those who violate social norms (Cosmides and Tooby 1992). Supporting this view, recent fMRI studies reported activation in brain regions such as the pSTS and MPFC during detection of the violation of social contracts (Canessa et al. 2005; Fiddick et al. 2005). Considering the functions of pSTS and MPFC, these regions might process intention of wrongdoings and, consequently, blameworthiness might be associated with the activation in pSTS.

The lack of activation in the pSTS and MPFC in response to moral beauty supports psychological studies in which people do not put a premium on the deliberate intention of commendable acts. Instead, correlation between the subjective ratings of praiseworthiness and the degrees of activation in the left OFC suggests that they regard positive outcome itself rather than intention of the act to be a main factor for praiseworthiness because the OFC is known to be involved in processing reward (Rolls 2006) and positive stimuli such as pictures (Northoff et al. 2000), taste (Small et al. 2003), and music (Blood and Zatorre 2001). It is also reported that the OFC was associated with maternal love (Bartels and Zeki 2004; Nitschke et al. 2004). The association between OFC activation and self-rating of praiseworthiness could be regarded as corresponding to Smith's phrase "The love of praiseworthiness" (Smith 1976).

Previous functional imaging studies have investigated the neural correlates processing facial beauty (Aharon et al. 2001; O'Doherty et al. 2003) or aesthetic beauty such as shapes or arts (Kawabata and Zeki 2004; Vartanian and Goel 2004; Jacobsen et al. 2006), and activation of reward-related subcortical and limbic areas including the OFC was reported. The connection between aesthetic judgment and moral feeling has long been emphasized in aesthetic theory (Kant 1952). Our finding could be interpreted in the context of aesthetic theory, that is, the neurocognitive system processing moral beauty might be related to that of aesthetic beauty.

We observed activation in other prefrontal areas in the left hemisphere, such as DLPFC and SMA, although activation in these unpredicted areas needs to be interpreted with caution. It is still unclear whether there is a hemispheric specialization in the processing of moral cognition, but it is suggested that frontal regions in the left hemisphere are associated with approach behavior, whereas frontal areas in the right hemisphere are associated with avoidance (Davidson 1992). Previous studies reported activation in the motor area in response to positive stimuli such as paintings, music, money, humor, and concepts (Blood and Zatorre 2001; Elliott et al. 2003; Mobbs et al. 2003; Kawabata and Zeki 2004; Cunningham et al. 2005). Although the exact role of the motor area in such tasks is not well known, it is suggested that the positive stimuli might mobilize the motor system to take some action toward them.

Although domain-specific emotional response is suggested to play a central role in moral judgments, domain-neutral reasoning could play certain roles as well (Haidt 2001; Greene and Haidt 2002). In a predictable situation, context-independent knowledge of event is processed automatically and routinely. This domain-specific process is suggested to be mediated in the medial and ventral prefrontal cortex. On the other hand, in a less predictable situation, context-dependent knowledge of event is processed with the operation of domain-neutral reasoning, which is suggested to be mediated in the DLPFC (Greene and Haidt 2002; Moll et al. 2005). It is also widely argued that emotions evolved to promote quick and automatic reaction in life-threatening situations (Fredrickson 1998). Although these models have been well fitted for negative emotions, quick and decisive actions are not typically required in a situation that gives rise to positive emotions. Instead, a wider range of thoughts or actions is required in situations where positive emotions occur (Fredrickson 1998). The DLPFC was reported to be recruited during evaluation of natural or

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artistic aesthetic stimuli (Cela-Conde et al. 2004). Although the exact role of the DLPFC in aesthetic evaluation remains unclear, our results suggested that context-dependent knowledge contributes to the evaluation of moral beauty.

In conclusion, evaluation of moral excellence and moral violation might be processed differently in the human brain. However, any generalization of our findings needs to be approached with caution as the social background of the participants, such as culture, generation, religion, and education, could affect the results. Still, our results suggest that humans might have developed different neurocognitive systems for evaluating blameworthiness (cheaters) and praiseworthiness (cooperators). Our finding might contribute to a better understanding of the neural basis of human morality.

Supplementary Matrial

Supplementary table S1 can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

Conflict of Interest: None declared.

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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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