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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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

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 $2 \times 2 \times 2$ 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. 1A). The MD − N condition produced activations in the left pSTS and MPFC (Table 1 and Fig. 1B). 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 2A and 3A). 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 2B and 3B). 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

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 depravity-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.
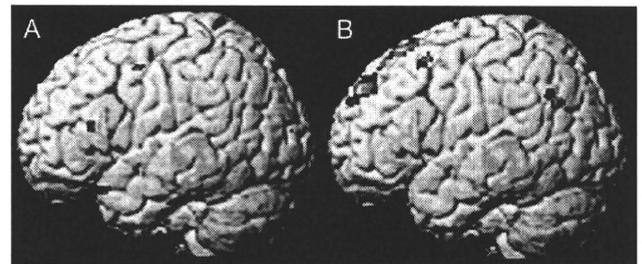

Figure 1. Images showing brain activations in response to (A) MB − N condition and (B) MD − N condition. (A) Significant activation in OFC is shown. (B) Significant activations in MPFC and pSTS are shown.
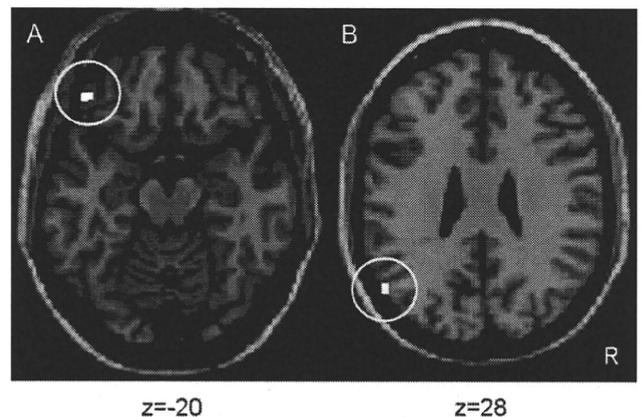

z=−20   z=28

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.

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.

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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 sub-cortical 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

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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

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 – N 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

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. 1A). The MD – N condition produced activations in the left pSTS and MPFC (Table 1 and Fig. 1B). 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 2A and 3A). 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 2B and 3B). 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

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 depravity-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.
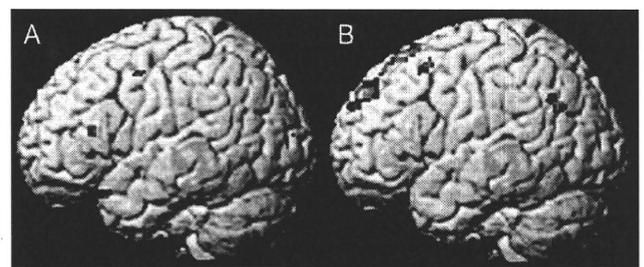

Figure 1. Images showing brain activations in response to (A) MB − N condition and (B) MD − N condition. (A) Significant activation in OFC is shown. (B) Significant activations in MPFC and pSTS are shown.
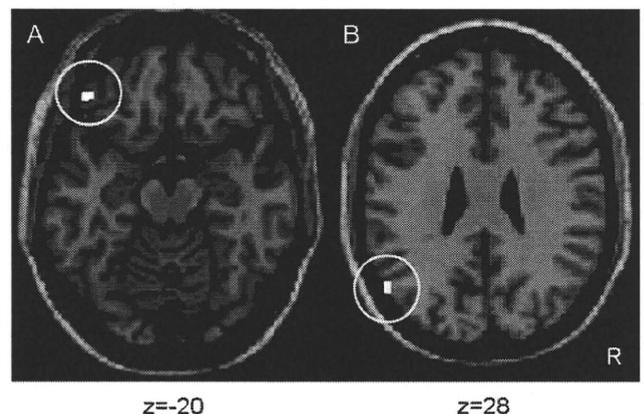

z=-20   z=28

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.

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.

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

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/.

Notes

Conflict of Interest: None declared.

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Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study

CINP

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Abstract

Previous studies of smoking on dopamine release in humans were investigated only in smokers. Using nicotine gum, we examined the effect of nicotine on dopamine release in smokers and non-smokers and its relation to the degree of nicotine dependence. Smokers and non-smokers participated in a double-blind, randomized, placebo-controlled cross-over study. They participated in two PET measurements with [¹¹C]raclopride, in which they received either nicotine or placebo. Changes in [¹¹C]raclopride non-displaceable binding potential (BP_{ND}) following nicotine administration were quantified. Smokers showed significant decrease in BP in the striatum following nicotine administration, but non-smokers did not show such a decrease. The BP_{ND} difference between the two scanning sessions was correlated with the degree of nicotine dependence. The BP_{ND} difference might reflect enhanced dopamine release in smokers and the reinforced effect of nicotine. These data suggest the feasibility of our gum method as well as the importance of the degree of dependence in future studies of the nicotine effect on the dopamine system.

Introduction

Nicotine is a major psychostimulant component of tobacco. Repeated nicotine exposure can induce nicotine dependence (Laviolette and van der Kooy, 2004; Olausson et al., 2003). It has been suggested that the mesolimbic dopamine pathway is involved in nicotine dependence (Yasuno et al., 2007). [¹¹C]raclopride has been used for the indirect measurement of changes in synaptic dopamine concentration in vivo using PET in response to addictive drugs like cocaine and amphetamine (Dewey et al., 1993). Dopamine is thought to compete with [¹¹C]raclopride at the D_2 receptor, and dopamine release is associated with

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a reduction in [¹¹C]raclopride binding (Dewey et al., 1993). Decreases in [¹¹C]raclopride binding potential (BP) in the ventral striatum have been demonstrated in smokers following cigarette smoking (Brody et al., 2004, 2006; Scott et al., 2007). On the other hand, two human PET studies of smokers (Barrett et al., 2004; Montgomery et al., 2007) and an awake-monkey study (Tsukada et al., 2002) showed no overall changes in [¹¹C]raclopride BP after exposure to nicotine. However, the monkeys were nicotine-naive, and the study by Montgomery et al. mainly examined low-dependence smokers. It can be expected that the degree of nicotine dependence affects dopamine release in the brain (Scott et al., 2007). In this study, we used nicotine gum with the aim of exposing non-smokers to nicotine to the same degree as smokers. Another objective of this pilot study was to examine the feasibility of nicotine gum methods. The study was conducted in a double-blind, randomized, placebo-controlled manner.

Method

Participants

Twelve male subjects (six smokers, mean age 25.8 ± 2.6 yr, and six non-smokers, 23.7 ± 2.7 yr) participated in a double-blind, randomized, placebo-controlled, cross-over pilot study. Smokers had a smoking history of at least 4 yr, with current use of $\geqslant 15$ cigarettes per day. The Fagerstrom test for nicotine dependence (FTND) was applied (Heatherton et al., 1991). The FTND, consisting of six questions (e.g. How soon after you wake up do you smoke your first cigarette? How many cigarettes per day do you smoke?), yields a score ranging from 0 to 10 (0–2, very low dependence; 8–10 very high dependence). The non-smokers had no history of recreational use of cigarettes. None of the subjects 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 (other than nicotine) dependence. MRI demonstrated intact cerebral structures in all subjects. All subjects were right-handed according to the Edinburgh Handedness Inventory. Smokers were instructed not to smoke for 24 h before scanning, and abstinence was verified by plasma nicotine measurement. Both before and after the administration of nicotine, the strength of cigarette craving was assessed using a 6-point scale (0 = no urge, 5 = extremely strong urge). After description of the study to the subjects, written informed consent was obtained, and the study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Japan.

Nicotine administration

Each subject participated in two PET sessions. To ensure maximum and stable plasma concentrations of nicotine during the PET scans, 1 h before each scan the subjects received two pieces of either nicotine (2 mg Nicorette, mint taste; Pfizer, Tokyo, Japan) or taste-matched placebo gum. A clinical research coordinator (Y.F.), generated the randomization sequence (the order of the two sessions) and packaged the placebo and nicotine gum in containers according to the balanced randomization list (half of the subjects took nicotine gum first, and the remaining half took placebo gum first). The participants and all study staff and investigators, except Y.F., remained blinded to the treatment allocation throughout the study. Every 3 min, the subjects chewed the gum five times at a rate of 1 Hz and then put the gum into the oral vestibule in front of the lower anterior teeth. Until the start of the PET

scans, the subjects were trained to chew the gum while not moving the maxilla but moving only the mandible in order to minimize head motion associated with jaw motion during mastication. The participants kept chewing the gum in the same way during the scans, and finally finished chewing at the end of the scans. Blood samples for measurement of plasma nicotine concentration were collected just before gum administration, and at 60 min, 75 min, 90 min, 105 min, and 120 min after gum administration.

PET scan

PET studies were performed on ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA). The system provides 63 planes and a 15.5-cm field of view. To minimize head movement, a head fixation device (Fixster, Stockholm, Sweden) was used. A transmission scan for attenuation correction was performed using a germanium-68–gallium-68 source. Acquisitions were performed in 3D mode with the interplane septa retracted. A bolus of 225.1 ± 9.7 MBq of [^{11}C]raclopride with a specific radioactivity of 262.0 ± 97.6 GBq/μmol was injected intravenously from the antecubital vein with a 20-ml saline flush. Dynamic scans were performed for 60 min immediately after the injection. All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (full width at half maximum, 7.5 mm). MRI was performed on Gyroscan NT (Philips Medical Systems, Best, The Netherlands) (1.5 T). T1-weighted brain images were obtained for all subjects. The scan parameters were 1-mm-thick, 3D T1 images with a transverse plane (repetition time/echo time, 19/10 ms; flip angle, $30°$; scan matrix, 256×256 pixels; field of view, 256×256 mm; number of excitations, 1).

Data analysis

The tissue concentration of radioactivity was obtained from volumes of interest (VOIs) defined on PET images with reference to the individual MRIs co-registered on summated PET images and a brain atlas. The regions were the right and left dorsal caudate, dorsal putamen, ventral caudate, and ventral putamen. Each VOI consisted of three slices. The dorsal boundary of the dorsal caudate was at the level of the interventricular foramen of Monro. The dorsal boundary of the dorsal putamen was two slices lower than that of the dorsal caudate. The ventral boundary of the ventral caudate was at the level of the lower boundary of the third ventricle. The ventral boundary of the ventral putamen was one slice higher than that of the ventral caudate. Quantitative analysis was

Table 1. [¹¹C]raclopride BP_{ND} (mean ± s.d.) in the striatal regions of smokers and non-smokers

	Smokers		Non-smokers	
	Placebo	Nicotine	Placebo	Nicotine
Right dorsal caudate	3.00 ± 0.16	2.87 ± 0.26	2.89 ± 0.48	2.93 ± 0.30
Left dorsal caudate	3.02 ± 0.22	2.85 ± 0.33	2.84 ± 0.36	2.93 ± 0.28
Right dorsal putamen	3.77 ± 0.33	3.52 ± 0.47	3.67 ± 0.39	3.62 ± 0.24
Left dorsal putamen	3.72 ± 0.39	3.50 ± 0.43	3.59 ± 0.42	3.65 ± 0.23
Right ventral caudate	2.74 ± 0.24	2.44 ± 0.18	2.47 ± 0.27	2.55 ± 0.29
Left ventral caudate	2.77 ± 0.26	2.52 ± 0.22	2.56 ± 0.36	2.62 ± 0.25
Right ventral putamen	3.66 ± 0.25	3.31 ± 0.21	3.27 ± 0.39	3.35 ± 0.32
Left ventral putamen	3.53 ± 0.40	3.30 ± 0.25	3.33 ± 0.43	3.41 ± 0.25
Striatal region[a]	3.28 ± 0.32	3.04 ± 0.24	3.08 ± 0.32	3.13 ± 0.24

BP_{ND}, Non-displaceable binding potential.

A three-way repeated-measure ANOVA revealed a significant drug × group interaction.

[a] Post-hoc analysis revealed that overall BP_{ND} values of the striatal region in the nicotine condition were significantly lower than in placebo in smokers. The BP_{ND} value of the striatal region is the mean of pooled data across ROIs. There was no main effect of subject group ($F_{1,10} = 0.12$, $p = 0.74$).

performed using the 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 dopamine D_2 receptors (Olsson et al., 1999; Suhara et al., 1999). The non-displaceable binding potential (BP_{ND}) (Innis et al., 2007) values were analysed using a three-way repeated-measures ANOVA with subject group (smokers, non-smokers) as a between-subjects factor and drug (nicotine, placebo) and ROI as within-subjects factors. Statistical significance of $p < 0.05$ was set for the analysis. To examine the relation between regional [¹¹C]raclopride BP_{ND} and the degree of nicotine dependence, Pearson correlation coefficients between the BP_{ND} of each VOI of both nicotine and placebo conditions and the FTND score were calculated. In addition, in order to explore the relation between nicotine-induced dopamine release and nicotine dependence, correlations between the change in [¹¹C]raclopride BP_{ND} of each VOI and FTND score were calculated. The threshold for significance was set at $p = 0.05/8 = 0.006$ to avoid type 1 errors. To investigate detailed regions, parametric images of BP_{ND} were analysed using SPM (Gunn et al., 1997). Paired t tests were used to compare the BP_{ND} maps following nicotine and placebo administration in both groups. Subtracting the normalized BP_{ND} image in the nicotine condition from that in the placebo condition, we created individual BP_{ND} change maps. Regression analyses were conducted to examine the relation between BP_{ND} change and nicotine dependence.

Results

Nicotine was not detected from any of the participants' plasma samples prior to the PET scans. During the PET scans, the plasma concentrations of nicotine using nicotine gum were 6–16 ng/ml, similar to those achieved by smoking a cigarette. There was no significant difference in the area under the nicotine plasma concentration–time curve (AUC) during PET scans between smokers and non-smokers. BP_{ND} of VOIs in both placebo and nicotine conditions are shown in Table 1. There was a significant drug × subject group interaction ($F_{1,10} = 6.42$, $p = 0.03$). Post-hoc analysis revealed that BP_{ND} values of the striatal region in the nicotine condition were significantly lower than in placebo in smokers ($F_{1,47} = 82.7$, $p < 0.001$) but not in non-smokers ($F_{1,47} = 1.99$, $p = 0.17$). Result of voxel × voxel parametric image analysis indicated significant BP_{ND} differences in the ventral caudate and putamen in smokers (Figure 1a). No significant correlation was found between the BP_{ND} of any VOI and FTND score in either the nicotine or placebo condition. However, the FTND score was correlated with the BP_{ND} difference between the two scanning sessions in the right ventral putamen ($r = 0.961$, $p = 0.002$). Trend-level correlations were observed between the FTND score and the BP_{ND} difference in the right ventral caudate ($r = 0.911$, $p = 0.012$) and the left ventral putamen ($r = 0.907$, $p = 0.012$). These correlations were also confirmed by parametric image analysis (Figure 1b). The BP_{ND} difference in the left ventral putamen
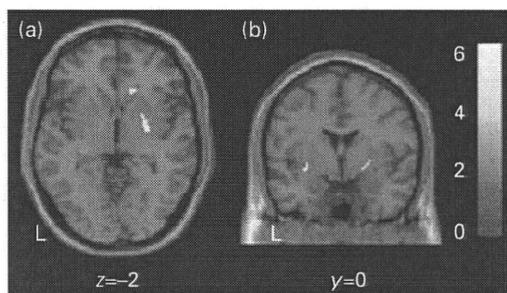
Figure 1. [^{11}C]raclopride non-displaceable binding potential (BP$_{ND}$) differences between the two scanning sessions in the striatum in smokers, and the correlation with nicotine dependence. (a) Image showing the significant [^{11}C]raclopride BP$_{ND}$ differences in the ventral caudate and putamen in smokers (height threshold at $p < 0.005$, uncorrected, and extent threshold of 10 voxels). (b) Image showing the correlation between the BP$_{ND}$ differences in the ventral putamen and the Fagerstrom test for nicotine dependence (FTND) score (height threshold at $p < 0.005$, uncorrected, and extent threshold of 10 voxels). The bar shows the range of the t value. Within the images, L indicates left. Numbers in the bottom row indicate the coordinates of the Montreal Neurological Institute brain.

was also correlated with the reduction in craving score ($r = 0.940$, $p = 0.005$). There was no significant correlation between the BP$_{ND}$ difference and the nicotine plasma concentration represented as AUC.

Discussion

This is the first double-blind, randomized, placebo-controlled study to investigate dopamine release following nicotine administration in both smokers and non-smokers. Smokers showed significant decreases in [^{11}C]raclopride BP$_{ND}$ in the striatum in response to nicotine, and such decrease is thought to reflect the dopamine release following nicotine administration (Brody et al., 2004, 2006). In line with previous studies, there was no significant difference in striatal [^{11}C]raclopride BP$_{ND}$ between smokers and non-smokers in either the nicotine or placebo condition (Scott et al., 2007; Yang et al., 2006). However, only smokers showed significant decreases in [^{11}C]raclopride BP$_{ND}$ in the striatum, while non-smokers showed no detectable changes. The dopamine release in the ventral striatum was correlated with the degree of nicotine dependence and the reduction of craving score in smokers. Enhanced dopamine release in smokers might be a result of the reinforced effect of cigarette smoking. Two human PET studies (Barrett et al., 2004; Montgomery et al., 2007) reported no

overall changes in [^{11}C]raclopride binding following nicotine administration in smokers. However, the majority of smokers in the latter study (Montgomery et al., 2007) were of low dependence and the plasma nicotine concentration was lower, whereas the majority of our smokers were moderately or highly dependent. In addition, those studies included female smokers, and gender differences in nicotine effects have been reported (Perkins et al., 1999).

As with other addictive drugs, animal studies have demonstrated that repeated nicotine administration enhances psychomotor responses, rewarding the effects of nicotine and striatal dopamine release in response to nicotine (Benwell and Balfour, 1992). Sensitization of the striatal dopamine response to nicotine has been implicated in the development of nicotine dependence (Benwell and Balfour, 1992).

Nicotinic acetylcholine receptors are expressed on both dopamine neurons and GABA neurons, and axon terminals of glutamatergic input to the midbrain (Laviolette and van der Kooy, 2004) and dopamine neurons in the midbrain are regulated by the balance of excitatory and inhibitory input to the midbrain (Mansvelder and McGehee, 2002). Chronic nicotine exposure was reported to reduce the sensitivity of GABA receptors and result in disinhibition of midbrain dopamine neurons (Amantea and Bowery, 2004). Chronic nicotine administration was also reported to increase the level of ionotropic glutamate receptors in the midbrain and conceivably enhance the excitatory input to the midbrain (Wang et al., 2007). Enhanced striatal dopamine release in smokers might be a consequence of altered control of dopamine release after repeated nicotine exposure.

In conclusion, compared to non-smokers, smokers showed enhanced striatal dopamine release in response to nicotine. The dopamine release in the ventral striatum following nicotine administration was correlated with the degree of nicotine dependence. Although this study is preliminary because of the limited sample, our findings were consistent with the report by Scott et al. (2007) with a similar sample size, suggesting both the feasibility of the nicotine gum method and the importance of the degree of dependence when examining the nicotine effect.

Acknowledgements

Statement of Interest

None.

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Regular Article

Enhanced activation in the extrastriate body area by goal-directed actions

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Aim: Neuroimaging studies on biological motion have established the view that the posterior superior temporal sulcus (pSTS) is involved in detecting intention of others. Those studies have consistently reported other regions such as body-selective extra-striate body area (EBA) and motion-sensitive middle temporal, in close proximity to pSTS. Whether EBA responds only to static body parts or has a more extended role as part of a system for inferring intention of others has remained an elusive issue. The aim of the present study was to investigate the role of EBA in processing goal-directed actions.

Methods: Twelve healthy volunteers participated in the present study. Using sports-related motions as visual stimuli, brain activations were examined during observation of goal-directed actions and non-goal-directed actions on functional magnetic resonance imaging.

Results: Compared to non-goal-directed actions, goal-directed actions produced greater activations in EBA along with the mirror neuron system.

Conclusions: EBA might contribute to understanding others' actions by representing the dynamic aspects of human motions.

Key words: extrastriate body area, fMRI, goal-directed actions, mirror neuron system, sports.

NEUROIMAGING STUDIES HAVE established the view that the posterior superior temporal sulcus (pSTS) plays a crucial role in processing biological motion,[1-4] and it has been suggested that the pSTS constitutes a part of the human mirror neuron systems (MNS) through which observed actions of others are internally represented,[5,6] and has a more general function in social cognition such as detecting intention of others[7-9] and behavior of agents.[3] But passive viewing of biological motion has consistently activated other regions of the posterior temporal–occipital cortex including body-selective extrastriate body area (EBA)[10] and motion-sensitive middle temporal (MT),[11] in close proximity to pSTS.[12-14]

Studies about biological motion have used point-light animation of simple action, and scrambled or occluded motion has been used in control condition. Therefore, the use of low-level stimuli as controls would make it difficult to clarify whether EBA and MT are, respectively, involved only in body and motion-sensitive low-level visual processing or lie in a part of a system for inferring the action and intention of others, such as STS. In the present study we compared brain activation in response to more complex meaningful biological motion with that to complex non-meaningful biological motion. We used sports-related motion and sports-unrelated motion for meaningful and non-meaningful biological motion,