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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.

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

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.

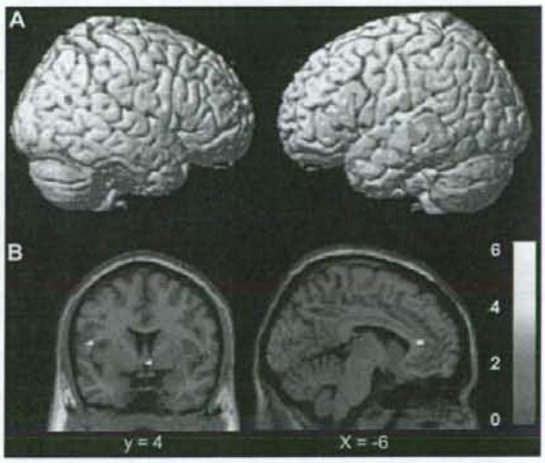

Figure 1. Images showing brain activation in joy and pride conditions relative to neutral condition. (*A*) Pride minus neutral. Activated regions were in the right posterior STS and left temporal pole. (*B*) Joy minus neutral. Activations in the ventral striatum, insula/operculum, and anterior cingulate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

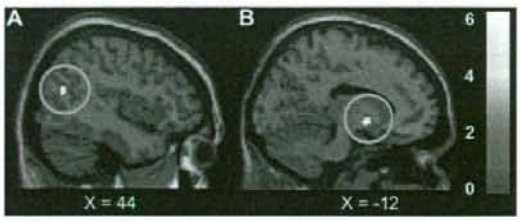

Figure 2. Correlation between brain activation and the self-ratings of pride and joy, with height threshold ($P < 0.001$) and extent threshold (5 voxels). (*A*) There was positive linear correlations between self-rating of pride and the degree of activation in the pSTS. (*B*) There was positive linear 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.

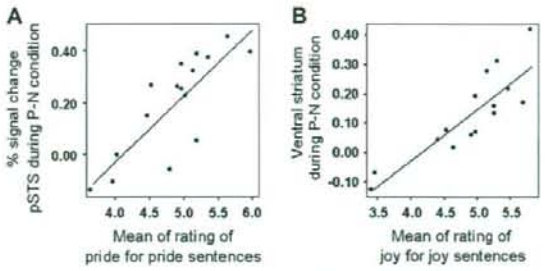

Figure 3. Plots and regression lines of correlations between self-ratings and the degree of activation in the brain regions. (*A*) Positive correlations ($r = 0.81$, $df = 14$, $P < 0.001$) between self-rating of pride and the degree of activation in the pSTS. (*B*) Positive linear correlations ($r =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

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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BRIEF REPORT

CINP

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

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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 [^{11}C]raclopride, in which they received either nicotine or placebo. Changes in [^{11}C]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.

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Key words: Dependence, dopamine, nicotine, positron emission tomography, striatum.

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). [^{11}C]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 [^{11}C]raclopride at the D_2 receptor, and dopamine release is associated with a reduction in [^{11}C]raclopride binding (Dewey et al., 1993). Decreases in [^{11}C]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 [^{11}C]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.

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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 ⩾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. [^{11}C]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 ($F_{1,16}=0.12$, $p=0.74$).

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 [^{11}C]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 [^{11}C]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 ($F_{1,16}=6.42$, $p=0.03$). 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

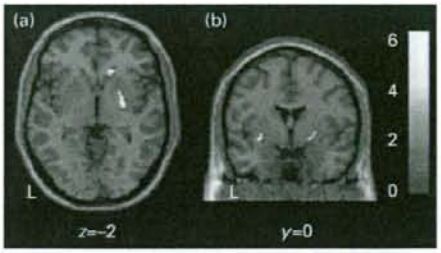

Figure 1. [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) differences between the two scanning sessions in the striatum in smokers, and the correlation with nicotine dependence. (a) Image showing the significant [^{11}C]raclopride BP_{ND} differences in the ventral caudate and putamen 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.

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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 extrastriate 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,

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respectively, because sports-related motion is meaningful and goal-directed, whereas sports-unrelated motion itself could be meaningful biological motion but become non-meaningful and non-goal-directed in the context of sports game rules. For example, carrying the ball with a certain aim in daily life or in a certain sport (e.g. rugby) is a natural and goal-directed action, but becomes non-goal directed when accompanied by the aim to win a soccer game, because handling the ball is against the rules of soccer.

Although the issues regarding the precise role of EBA are still controversial,[15] recent studies have suggested an extended role for the EBA, involving not only static visual perception of body parts but also the planning, execution and imagination of actions,[16,17] and that the EBA is located at the entry of the human MNS.[17,18] We hypothesized that sports-related goal-directed motion would produce greater activation than sports-unrelated non-goal-directed motion in EBA along with STS and MNS.

METHODS

Participants

Twelve healthy volunteers (mean age 29.4 ± 4.5 years) participated in the present study. All subjects were Japanese and right-handed. All participants had played basketball in elementary or junior high school, but did not play basketball regularly thereafter. The participants were free of any criteria for neuropsychiatric disorders based on unstructured psychiatric screening interviews. None of the participants was 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 magnetic resonance imaging 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

Two types of video clips were provided (basketball-related [BR] and basketball-unrelated [BU] motion). Examples of the video clips are shown in Fig. 1. Because a series of basketball plays consists of several actions and several players, it is difficult to provide a natural stream of control video clips (BU motion) consisting of identical numbers and directions of actions to BR motion. Therefore, we used some actions that are the components of a series of actions of a basketball game, aiming to make it easier to provide control actions (BU motion). BR motion consisted of three types of scenes (player shooting a free throw, player dribbling, two players performing man-to-man defense/offence). BU motion also consisted of three types of scenes (player rolling a basketball, player carrying a basketball, one player crossing in front of another without interaction). In order to make BR and BU motion as similar as possible, all players in the video clips performed in front of a basket goal on a basketball court, and the number of persons, objects, motion direction and speed were matched, that is, rolling a basketball, carrying a basketball, and crossing in front of another without interaction corresponded to shooting a free

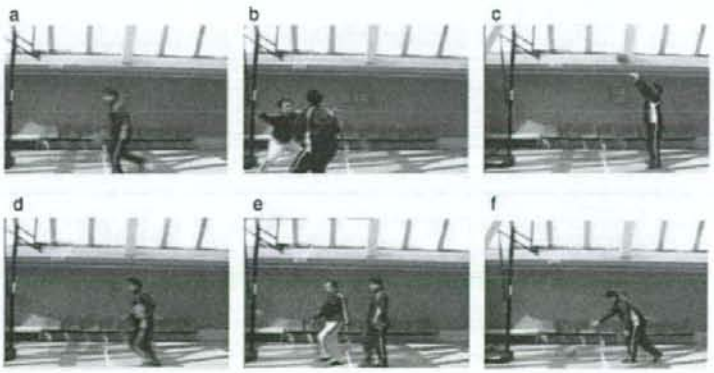

Figure 1. Sample of still frames from (a–c) basketball-related motions and (d–f) basketball-unrelated motions. (a) Dribbling; (b) man-to-man; (c) shooting; (d) carrying; (e) crossing; (f) rolling.

throw, dribbling, and man-to-man defense, respectively. The video clips were projected via computer and telephoto lens onto a screen mounted on a head-coil. The subjects were instructed to pay attention to the video clips and to press a selection button with the right index finger when they watched the free-throw scene and the basketball-rolling scene, indicating that they had paid attention to them. The experimental design consisted of five blocks for each of the two conditions (BR and BU motion) interleaved with 20-s rest periods. During the rest condition, participants viewed a crosshair pattern projected to the center of the screen. In the BR and BU motion 24-s blocks, three scenes were presented twice for 4 s each. The order of BR and BU motion conditions was fixed across the subjects.

Image acquisition

Images were acquired with a 1.5-Tesla Signa system (General Electric, Milwaukee, WI, USA). Functional images of 115 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to blood oxygenation level-dependent (BOLD) 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°; TE, 50 ms; TR, 4 s; matrix, 64 × 64; field of view, 24 × 24 cm). High-resolution, T1-weighted anatomic images were acquired for anatomic comparison (124 contiguous axial slices, 3-D spoiled gradient-recalled acquisition in a steady state 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 using a statistical parametric mapping software package (SPM02; Wellcome Department of Cognitive Neurology, London, UK) running with MATLAB (Mathworks, Natick, MA, USA). 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 $2 \times 2 \times 2$ mm^3. Functional images were spatially smoothed with a 3-D isotropic Gaussian kernel (full width at half maximum, 8 mm). Low-frequency noise was removed by applying a high-pass filter (cut-off period, 192 s) to the functional MRI (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 BR motion minus BU motion. 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. Contrast images were obtained from single-subject analysis and entered into group analysis. A one-sample *t*-test was applied to determine group activation for each effect. A statistical threshold of $P < 0.05$ corrected for multiple comparisons across the whole-brain was used, except for a priori hypothesized regions thresholded at $P < 0.001$ uncorrected (only clusters involving ≥10 contiguous voxels are reported). These a priori regions of interest included the biological motion-related regions (STS, MT and EBA), human MNS (inferior parietal lobule [IPL] and inferior frontal cortex). We also assessed the contrasts of BU motion minus BR motion to investigate possible brain activations in response to the BU motion condition relative to BR motion condition.

RESULTS

Behavioral results

All subjects paid attention to the video clips and pressed the button appropriately (100% accuracy).

FMRI results

BR motion minus BU motion condition produced activations in the bilateral posterior temporal–occipital cortex including bilateral EBA ($x = 58$, $y = -60$, $z = 2$, $t = 4.86$) and MT ($x = 54$, $y = -66$, $z = -12$, $t = 8.38$), right STS ($x = 56$, $y = -22$, $z = -2$, $t = 6.58$), bilateral premotor cortex ($x = -48$, $y = -4$, $z = 40$, $t = 4.94$), and bilateral IPL ($x = -34$, $y = -50$, $z = 54$, $t = 7.25$; coordinates and t-score refer to the peak of each brain region; Fig. 2). A one-sample *t*-test of BU motion minus BR motion contrasts indicated no significant activation at a height threshold of

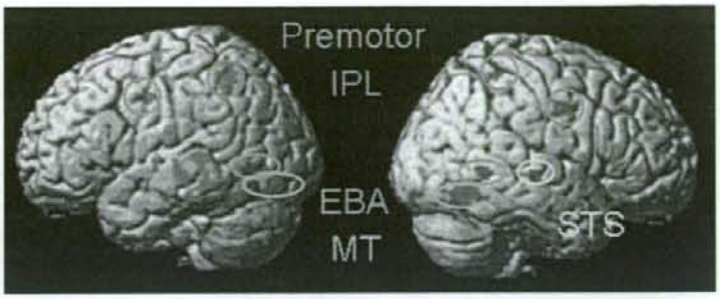

Figure 2. Brain activations in response to sports-related motion minus sports-unrelated motion. Significant activations in extrastriate body area (EBA), middle temporal (MT), superior temporal sulcus (STS), inferior parietal lobule (IPL) and premotor areas are shown. Within the images, L indicates left and R indicates right.

$P < 0.001$, uncorrected, and an extent threshold of 10 contiguous voxels.

DISCUSSION

This study demonstrated that BR motion produced greater activation in the posterior temporal–occipital cortex (MT and EBA), STS and IPL than BU motion. BR motion was complex goal-directed biological motion with understandable intention, whereas BU motion was complex non-goal-directed biological motion. Therefore, the greater activation of STS was fairly predicted because it is widely accepted that STS is involved in detection of goal-directed actions and intention of others,[3,8,9] and even a walking robot could activate STS.[19] The greater activation of IPL, as a part of human MNS, was also predicted. Human neuroimaging and monkey studies have supported the view that when we observe others' actions, the action is internally represented through our own motor system including MNS.[5,18,20] It has been suggested that MNS may participate in understanding and imitation of action through a mechanism by which observed actions are automatically matched with internal motor representation (action repertoire),[5,6,21–23] and IPL neurons respond differently to similar actions with various intentions.[24]

The novel finding in the present study is that EBA and MT responded more strongly to BR motion than BU motion, although both BR motion and BU motion were complex biological motions containing an identical number of bodies or body parts. Neuroimaging studies about biological motion have demonstrated that STS plays a crucial role in processing biological motion and is important for detecting intention of others. But the studies have consistently reported the involvement of other brain regions such as EBA and MT,[25,26] and the exact role of these regions in processing biological motion has been unclear.

Originally, EBA was identified as an area that responds selectively to human bodies and body parts. In that study, at the same time, EBA responded more strongly to natural motion than to artificial motion.[10] Thereafter, the role of EBA in processing human actions has been the focus of many discussions. The static representation hypothesis is that EBA responds simply to static snapshots of the individual posture that comprise whole-body actions.[27] In contrast, the dynamic representation hypothesis is that EBA is directly involved in representing the dynamic aspects of human motions as part of a system for inferring the action and intention of others.[17,18] Astafiev *et al.* demonstrated that EBA also responded to self-produced body movements, even if the body part is not visible.[16] Jackson *et al.* reported that, compared to observation of actions, EBA activation was enhanced during imitation.[17] Furthermore, the motivation to act has been shown to modulate EBA activity.[28] These studies proposed an extended role for EBA, involving the planning, execution and imagination of actions. In favor of the latter hypothesis, the present result suggests that EBA might contribute to the understanding of goal-directed actions, being located at the entry of human MNS.

MT has been known to respond selectively to moving stimuli,[11] and an fMRI study reported that MT responded equally to meaningful and non-meaningful actions,[19] suggesting that MT processes low-level physical properties or information of moving stimuli. But it was reported that MT responded to static images of implied motion[29] and that the MT responses to static body images were greater than to other object images.[30,31] From these findings it is suggested that face and body figural information might project to MT.[26,32] The present findings of enhanced activations in MT along with EBA may support this view, although several studies have reported substantial overlapping between EBA and MT.[14,30,31]

In conclusion, EBA might be located at the entry of human MNS through which dynamic aspects of human motions are represented and contribute to the understanding of others' actions. The present results merit further investigation of the function of EBA in neuropsychiatric disorders such as schizophrenia and autism.

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Regional dopamine synthesis in patients with schizophrenia using L-[β-^{11}C]DOPA PET

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ABSTRACT

The dopamine hypothesis has been the most widely known theory concerning schizophrenia. However, the exact mechanism including presynaptic dopaminergic activity and its relationship with symptom severity still remains to be revealed. We measured presynaptic dopamine synthesis using positron emission tomography (PET) with L-[β-^{11}C]DOPA in 18 patients with schizophrenia (14 drug-naïve and 4 drug-free patients) and 20 control participants. Dopamine synthesis rates, expressed as k_i values, were obtained using a graphical method, and the occipital cortex was used as reference region. Regions of interest were placed on the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). We found significantly higher k_i values in patients than in controls in the left caudate nucleus, but not in the other regions. The k_i values in the thalamus exhibited a significant positive correlation with the PANSS total scores. Furthermore, a significant positive correlation was observed between the PANSS positive subscale scores and k_i values in the right temporal cortex. Patients with schizophrenia showed higher dopamine synthesis in the left caudate nucleus, and dopaminergic transmission in the thalamus and right temporal cortex might be implicated in the expression of symptoms in schizophrenia.

1. Introduction

Positron emission tomography (PET) has allowed us to investigate the dopamine hypothesis in living human brain. Since there is no ideal animal model of schizophrenia, PET investigation is still the most useful method for investigating neurotransmission in patients. As for postsynaptic dopaminergic receptors, several studies have investigated striatal (Farde et al., 1990; Nordström et al., 1995; Wong et al., 1986) and extrastriatal (Suhara et al., 2002; Yasuno et al., 2004) D_2 receptor (D_2R) binding by the use of PET. Although studies investigating D_2R in the striatum in schizophrenia have reported inconsistent findings, those focusing on extrastriatal D_2R binding have repeatedly reported its reduction in the anterior cingulate cortex (Suhara et al., 2002) and the thalamus in schizophrenia (Talvik et al., 2003; Yasuno et al., 2004). Regarding intrasynaptic function, striatal dopamine release was reported to be enhanced in schizophrenia (Breier et al., 1997; Laruelle et al., 1996). On the other hand, many studies did not find any change in dopamine transporter binding in the striatum of schizophrenia (Laakso et al., 2000;

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Laruelle et al., 2000; Schmitt et al., 2005; Yang et al., 2004). These findings suggest that patients with schizophrenia may have elevated presynaptic dopamine synthesis, and investigations on presynaptic dopaminergic function in extrastriatal regions might be critical for providing an understanding of the pathophysiology of schizophrenia.

Radiolabeled L-DOPA, a precursor of dopamine, has been used to investigate presynaptic dopamine synthesis. L-DOPA is transported through the blood–brain barrier (BBB), taken up by presynaptic monoaminergic neurons, and metabolized to dopamine by aromatic amino acid decarboxylase (AADC). Previous studies on the dopamine synthesis of schizophrenia used 6-[^{18}F]fluoro-L-DOPA (Dao-Castellana et al., 1997; Elkashef et al., 2000; Hietala et al., 1995, 1999; McGowan et al., 2004; Reith et al., 1994;) or L-[β-^{11}C]DOPA (Gefvert et al., 2003; Lindström et al., 1999). The studies with 6-[^{18}F]fluoro-L-DOPA, which is widely used in schizophrenia research, indicated elevated dopamine synthesis (Hietala et al., 1995, 1999; Lindström et al., 1999; McGowan et al., 2004; Reith et al., 1994), elevated dopamine turnover (Kumakura et al., 2007), only higher variability (Dao-Castellana et al., 1997), and even reduced synthesis (Elkashef et al., 2000) in the striatum.

The 3-O-methyl metabolite of L-DOPA crossing the BBB can reportedly cause an error in quantification of the dopamine synthesis rate (Dhawan et al., 1996; Melega et al., 1990; Wahl et al., 1994). However, 3-O-methylation of L-[β-^{11}C]DOPA does not take place readily and rapidly when compared with 6-[^{18}F]fluoro-L-DOPA (Ito et al., 2006; Melega et al., 1990; Torstenson et al., 1999). Recently, we evaluated the accuracy of quantitative analyses of L-[β-^{11}C]DOPA PET studies (Ito et al., 2006). In the current study, we investigated regional dopamine synthesis and its relationship with the severity of positive and negative symptoms in patients with schizophrenia using L-[β-^{11}C]DOPA.

2. Methods

2.1. Participants

Fourteen (8 males and 6 females) drug-naïve and 4 (2 males and 2 females) 3-month drug-free patients (35.6± 7.4 years, mean±SD) meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia or schizophreniform disorder were recruited from the outpatient units of university hospitals, their affiliated psychiatric hospitals, and a mental clinic. On the day of the PET study, the diagnosis was re-evaluated by 3 experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The severity of psychotic symptoms was also evaluated by the same 3 psychiatrists with the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Igarashi et al., 1998). Each interview was conducted by 2 of 3 authors (S.N., F.Y., M.O.) and one other psychiatrist. Patients with schizophreniform disorder (2 males and 2 females) at the time of the PET study were followed up for at least 6 months from onset, confirming that they eventually met the criteria of schizophrenia. Twenty (10 males and 10 females) healthy volunteers (35.1±9.5 years) were recruited as controls through public notices. All the subjects were examined by physicians to obtain data concerning their educational background as well as current and past medical problems, and family history by unstructured interview and a general questionnaire. Handedness was assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971). The control subjects were matched with the patients for age, gender, education, and handedness. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. The demographic characteristics of all participants are shown in Table 1. Exclusion criteria of patients and controls were as follows: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse including alcohol; (3) previous episodes of mood disorder. One patient was excluded because of a large cyst in the cerebellum (data not shown).

After giving explanation of the study, written informed consent was obtained from all patients and control subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

2.2. PET study

All the participants were instructed to fast for 4 h before PET scan in order to avoid the influence of the plasma concentration of neutral amino acid (NAA) on the L-[β-^{11}C]DOPA uptake rate. A PET scanner (ECAT EXACT HR, CTI-Siemens, Knoxville, TN), providing 63 planes with an axial field of view of 15.5-cm, was used. A head fixation device (Fixster, Stockholm Sweden) was used to minimize head movement. A transmission scan for attenuation correction was performed using a ^{68}Ge–^{68}Ga source. Data acquisition was performed in 3-dimensional mode with the interplane septa retracted. A bolus of 331.5 to 401.8 MBq (373.0±14.1 MBq, mean±SD) of L-[β-^{11}C]DOPA with specific radioactivities (9.9–156.4 GBq/μmol) was injected intravenously via the antecubital vein and flushed rapidly with 20 mL of saline. Dynamic scans were performed for 64 min immediately after the injection. The scanning sequence consisted of seven 1-min frames, five 2-min frames, four 3-min frames, and seven 5-min frames. All emission scan data were reconstructed with a Hanning filter with a cutoff frequency of 0.4 (final in-plane resolution: 7.5 mm full width at half maximum).

Table 1
Demographic and clinical characteristics of patients with schizophrenia and normal controls

	Controls (n=20)	Patients (n=18)
Gender, M/F	10/10	10/8
Age, y, mean±SD	35.1±9.5	35.6±7.4
Range	20–55	20–52
Medication, no. naïve (M/F)/free (M/F)		14 (8/6)/4 (2/2)
Handedness, no. right/left	20/0	18/0
Education, y, mean (range)	15.1 (12–9)	14.1 (9–16)
No. of smokers (M/F)	4 (4/0)	6 (4/2)
Duration of illness, mo, mean (range)		26.4 (1–120)
PANSS		
Whole score		
Mean±SD		79.2±21.4
Range		46–124
Subscales		
Positive (mean±SD)		22.6±7.3
Negative (mean±SD)		17.1±6.5
General psycho (mean±SD)		39.6±11.0

Table 2
k_i values of each ROI in patients with schizophrenia and normal controls

Region	L/R	Controls	Patients	ANCOVA#	
		(n=20)	(n=18)	F	p
Parahippocampus	L	4.54±1.13	4.91±1.45	0.704	0.407
	R	4.76±1.11	4.47±1.29	0.528	0.472
Temporal cortex	L	1.92±0.99	1.98±0.81	0.041	0.842
	R	1.86±0.83	1.92±0.87	0.037	0.849
Prefrontal cortex	L	1.31±0.73	1.22±0.64	0.324	0.573
	R	1.35±0.73	1.35±0.57	0	1.000
Thalamus	L	3.55±1.60	3.19±1.72	0.549	0.463
	R	3.11±1.45	3.09±1.54	0.001	0.970
Putamen	L	15.52±2.04	15.76±2.14	0.139	0.711
	R	15.39±2.31	14.90±3.01	0.329	0.570
Caudate	L	12.89±2.68	14.66±2.38	4.409	0.043*
	R	13.71±2.74	13.59±2.09	0.026	0.872
Anterior cingulate	L	2.74±1.33	3.05±1.50	0.445	0.509
	R	3.24±1.73	3.00±1.13	0.288	0.595

Dopamine synthesis rates, expressed as $k_i \times 1000$, were presented as mean± standard deviation.
#: Analysis of covariance with age as covariate (df= 1, 35).
L indicates left and R indicates right. The symbol * represents $p<0.05$.

2.3. Magnetic resonance images

For each participant, a structure magnetic resonance (MR) image was obtained. All MR imaging studies were performed with a 1.5-Tesla MR scanner (Philips Medical Systems, Best, The Netherlands). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin transverse sections (echo time, TE: 9.2 ms; repetition time, TR: 21 ms; flip angle: 30°; field of view: 256 mm; acquisition matrix: 256×256; slice thickness: 1 mm).

2.4. Data analysis

All MR images were coregistered to the PET summation images of all frames using statistical parametric mapping 2 (SPM2; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Regions of interest (ROIs) were drawn on the coregistered MR images, referring to the human brain atlas (Mai et al., 1997), and then transferred to the PET images. ROIs were defined for the prefrontal cortex, temporal cortex, anterior cingulate, parahippocampus, thalamus, caudate nucleus, and putamen. The ROIs were set on both left and right sides of the brain and those values were independently evaluated. To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

The overall uptake rate constant k_i of L-[β-^{11}C]DOPA, which indicates the net dopamine synthesis rate, was determined for each ROI by the graphical plot analysis method developed by Gjedde and Patlak (Gjedde, 1982; Ito et al., 2006; Patlak and Blasberg, 1985). k_i values can be estimated by simple linear least-squares fitting as follows:

$$\frac{C_i(t)}{C_i'(t)} = k_i \frac{\int_0^t C_i'(\tau)d\tau}{C_i'(t)} + F_{t>t^*}$$

where C_i is the total radioactivity concentration in a brain region that can be measured by PET, C_i' is the total radioactivity concentration in the reference brain region with no irreversible compartments, and t^* is the equilibrium time of the compartment for unchanged radioligand in the brain tissue. Plotting $C_i(t)/C_i'(t)$ versus $\int_0^t C_i'(\tau)d\tau/C_i'(t)$, after the time t^*, yields a straight line with the slope k_i and intercept F. In the present study, the occipital cortex was used as reference region (Ito et al., 2006). A range of equilibrium time t^* of 31.5 to 61.5 min was used.

ROI analyses were independently performed by 3 researchers who were blinded to the diagnoses. The intraclass correlation coefficient across all ROIs was 0.976 (McGraw and Wong, 1996), considered as excellent. In order to reduce variance, the k_i values by one researcher that most frequently showed medium values among those obtained by the 3 researchers were used for the following analyses.

2.5. Statistical analysis

Demographic variables were compared by independent sample t-test or chi-square test. Differences in the k_i values for each of the 7 × 2 brain regions between patients and controls were evaluated by one-way univariate analyses of covariance with age as a covariate, since an effect of age on k_i values has been reported (Ota et al., 2006). Pearson's correlation coefficients were calculated between the PANSS scores and k_i values. A significance level of $p<0.05$ (two-tailed) was used both in the comparison analyses between groups and in the correlation analyses.

3. Results

3.1. Demographic data

The demographic data of schizophrenia patients and controls are shown in Table 1. There were no significant differences between patients and controls in terms of age, gender, education, handedness, and the injected dose and

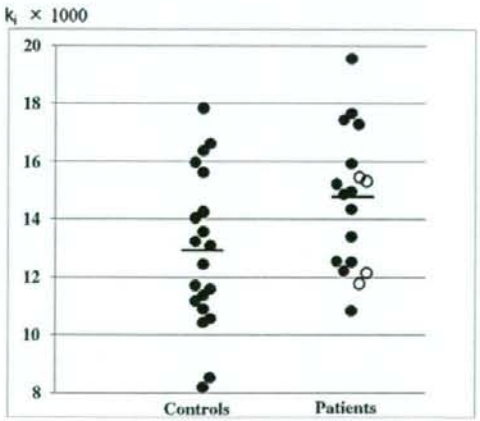

Fig. 1. Comparison of k_i values between patients with schizophrenia and control subjects in the left caudate nucleus. Horizontal lines represent mean values of the groups. Among patients, the closed circles indicate the values of antipsychotic drug-naïve patients, whereas the open circles indicate those of drug-free patients.