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Brain activation associated with evaluative processes of guilt and embarrassment: an fMRI study

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We aimed to investigate the neural substrates associated with evaluative process of moral emotions. Using functional magnetic resonance imaging (fMRI), we examined the similarities and differences between evaluative process of guilt and that of embarrassment at the neural basis level. Study of the neural basis of judgments of moral emotions might contribute to a better understanding of the amoral behavior observed in neurological and psychiatric disorders. Nineteen healthy volunteers were studied. The participants read sentences carrying neutral, guilty, or embarrassing contents during the scans. Both guilt and embarrassment conditions commonly activated the medial prefrontal cortex (MPFC), left posterior superior temporal sulcus (STS), and visual cortex. Compared to guilt condition, embarrassment condition produced greater activation in the right temporal cortex (anterior), bilateral hippocampus, and visual cortex. Most of these regions have been implicated in the neural substrate of social cognition or Theory of Mind (ToM). Our results support the idea that both are self-conscious emotions, which are social emotions requiring the ability to represent the mental states of others. At the same time, our functional fMRI data are in favor of the notion that evaluative process of embarrassment might be a more complex process than that of guilt.

Keywords: Guilt; Embarrassment; Social cognition; Theory of Mind; Medial prefrontal cortex; Superior temporal sulcus

Introduction

Although there have been numerous neuroimaging studies on primary emotions (fear, disgust, happiness, and sadness) that have led to a better understanding of the neuroanatomical correlates of emotions (Phan et al., 2002), only a few studies on complex social emotions such as guilt, shame, and embarrassment have been reported. These social emotions have been viewed as moral emotions because they occur in response to moral violation and promote moral behavior, interpersonal etiquette, and personal hygiene (Eisenberg, 2000; Haidt, 2003). At the same time, these emotions inhibit transgression of social standards and motivate reparative action such as apology, confession, and atonement.

Impairment of possessing the mental states of these moral emotions could lead to amoral, inappropriate behaviors observed in neurological and psychiatric disorders such as brain injuries (Anderson et al., 1999; Beer et al., 2003), frontotemporal dementia (Miller et al., 2003; Snowden et al., 2002), autism (Capps et al., 1992; Frith, 2001; Hillier and Allinson, 2002), and antisocial personality (Brower and Price, 2001; Moll et al., 2003). Studying the neural substrates of judgments of moral emotions should add to the understanding of the neural basis of amoral behaviors observed in neurological and psychiatric disorders.

From a psychological point of view, guilt, shame, embarrassment, and pride are categorized into the same emotion family, "self-conscious emotions". "Self-conscious emotions" are emotions founded in social relationship and arise from concerns about others' opinions of self or the behavior of self (Eisenberg, 2000; Haidt, 2003; Tangney and Dearing, 2002). Negative evaluation of self or the behavior of self is fundamental to guilt, shame, and embarrassment, while positive evaluation of self leads to pride. In other words, one needs the ability to represent the mental states of others (intention/emotion), that is, Theory of Mind (ToM), to recognize self-conscious emotions. The recognition of negative self-conscious emotions involves understanding of the violation of social norms and the negative evaluation of self, both important aspects of ToM. Children with autism demonstrating impaired ToM showed impaired recognition of self-conscious emotions (Heerey et al., 2003). In line with this notion, a recent functional magnetic resonance imaging (fMRI) study demonstrated activation in the medial prefrontal cortex (MPFC), temporal regions, and orbito-

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frontal cortex (OFC) during the emotional judgments of embarrassment (Berthoz et al., 2002). These areas have been implicated in ToM, social cognition, and moral judgment (Adolphs, 2001; Allison et al., 2000; Frith, 2001; Frith and Frith, 1999; Greene and Haidt, 2002; Greene et al., 2001; Moll et al., 2003; Pinkham et al., 2003). However, a previous positron emission tomography (PET) study using a guilt-related script reported a slightly different activation pattern in anterior paralimbic regions during the experience of guilt (Shin et al., 2000). In the former fMRI study, an emotional judgment task was used. Participants read various kinds of stories depicting embarrassing situations and were instructed to imagine what the story protagonist (participant himself or a third person in the story) would feel. In the latter PET study, an emotion induction method was used. Participants listened to audio-taped personal events involving the most guilt they had actually experienced. They recalled and imagined the event as if they were actually participating in it again. These two studies differed in the emotional tasks and measurement methods, making it difficult to compare the results directly. To our knowledge, no neuroimaging study has as yet investigated the different types of self-conscious emotions and compared the neural activation patterns directly in one session.

Although the distinctions among guilt, shame, and embarrassment are not clear-cut, psychologists have challenged this issue. Although embarrassment has traditionally been considered to be a variant of shame (Lewis, 1993), recent psychological data support the notion that embarrassment is an emotion distinct from other self-conscious emotions (Keltner and Buswell, 1997). Embarrassment has higher affinity to violation of social conventions, while guilt and shame have higher affinity to violation of a moral norm (Eisenberg, 2000; Haidt, 2003; Tangney et al., 1996). In this sense, among the negative self-conscious emotions, distinction between guilt and embarrassment is considered to be relatively clear-cut. Therefore, we focused on these two emotions.

We used block-design fMRI to measure regional activation associated with judgments of guilt and embarrassment during an emotional judgment task presenting short sentences. Emotion processing is composed of evaluative, experiential, and expressive components. We did not intend to induce emotional states because we thought it would be difficult to induce emotional states of guilt or embarrassment by merely having the subjects read short sentences. Moreover, it would be difficult to control the situation so as not to induce emotions other than guilt and embarrassment (e.g., anger, shame, sadness) as reported in the previous induction study (Shin et al., 2000). We aimed to elucidate the similarities and differences between the evaluative process of guilt and that of embarrassment at the neural basis level by measuring neural activation during judgments of both emotions in a session using fMRI.

We hypothesized that both emotional conditions would commonly activate the components of the neural substrates (MPFC, superior temporal sulcus (STS)) that have been implicated in social cognition (Adolphs, 2001; Allison et al., 2000) or ToM (Frith, 2001; Frith and Frith, 1999), and at the same time, would show differences in the extent of activation of the components.

Method

Participants

Nineteen healthy right-handed Japanese subjects (10 men, mean age 30.8 years, SD = 6.2; nine women, mean age 25.1 years, SD = 3.2) were recruited from the surrounding community. Their mean educational achievement level was 16.2 years (SD = 2.1). They did not meet criteria for any psychiatric disorder. 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

Because our experimental design was a block design, we aimed to control readability, the number of words, and luminance across blocks using short sentences. In addition, we expected participants to make emotional judgments repeatedly in a block. For this reason, we used short sentences instead of other forms, for example, stories. Three types of short sentences were provided (neutral, guilt, and embarrassment). Each sentence was written in Japanese and in the first person, past tense. Each sentence was expected to carry guilt, embarrassment, or no prominent emotional content. To validate our expected results, other healthy volunteers (10 men and 10 women, mean age 28.6 years, SD = 3.7) than the subjects participating in this fMRI study were screened. They read each sentence and rated the described situations according to how guilty or embarrassing they seemed using a 6-point analog scale (1 = none, 6 = extremely intense). As we predicted, the mean ratings of guilt and embarrassment for neutral sentences were 1.0 (SD = 0.1) and 1.0 (SD = 0.1), for guilt-related sentences 4.4 (SD = 0.4) and 1.6 (SD = 0.4), and for embarrassing sentences 1.5 (SD = 0.3) and 3.5 (SD = 0.5), 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 that they would rate the described situations according to how guilty or embarrassing they seemed. 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 six blocks for each of the three conditions (neutral, guilt, and embarrassment) interleaved with 20-s rest periods. The order of presentation for the three conditions was fixed in the neutral–guilt–embarrassment sequence (Fig. 1). During the rest condition,

Table 1
Examples of sentences

Neutral	I used a cellular phone in the park.
	I used a computer on the internet.
	I change into pajamas at night.
	I washed my clothes.
	I had dinner at the restaurant.
Guilt	I used a cellular phone in the hospital.
	I sent a computer virus by e-mail.
	I shoplifted a dress from the store.
	I betrayed my friend.
	I left the restaurant without paying.
Embarrassment	I was not dressed properly for the occasion.
	I mistook a stranger for my friend.
	I noticed that the zipper of my pants was open.
	I soiled my underwear.
	I did not know the right behavior at the restaurant.

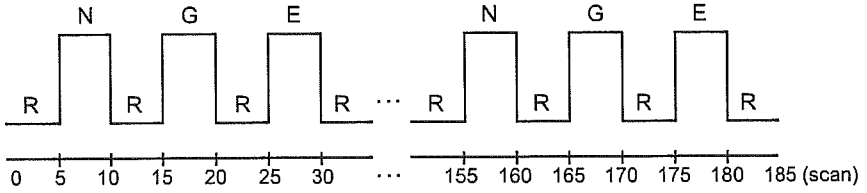

Fig. 1. Block design paradigm in the fMRI study. R = rest, N = neutral, G = guilt, E = embarrassment.

participants viewed a crosshair pattern projected to the center of the screen. In each 20-s block, five different sentences of the same emotional class were presented for 4 s each. After the scan, subjects rated the described situations according to how guilty or embarrassing they seemed using a 6-point analog scale.

Image acquisition

Images were acquired with a 1.5-T Signa system (General Electric, Milwaukee, WI). Functional images of 185 volumes were acquired with T2*-weighted gradient echo planar imaging sequences sensitive to the 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, 3D Spoiled-Grass sequence (SPGR), 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 (SPM99) (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 (MNI) 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 = 240 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. The t values were then transformed to unit normal distribution, resulting in Z scores.

To assess the specific condition effect, we used the contrasts of guilt minus neutral (G − N) and embarrassment minus neutral (E − N). A random effects model, which estimates the error variance for each condition across 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 were entered into the group analysis. A one-sample t test was applied to determine group activation for each effect. Significant clusters of activation were determined using the conjoint expected probability distribution of the height and extent of Z scores with the height ($Z > 3.09$; $P <$

Table 2
Brain activation in guilt condition and embarrassment condition relative to neutral condition

Brain region	Coordinates			BA	Z score	Voxels
	x	y	z			
Guilt minus neutral						
L visual cortex (cuneus, LG)	−6	−95	12	17,18,19	4.55	1114
R visual cortex (LG)	2	−85	6	17,18	5.41	
L MPFC (MFG, SFG)	−16	49	9	6,8,9,10	4.7	1175
R MPFC (MFG)	4	57	16	9,10	3.62	
L posterior STS (MTG)	−44	−61	20	39	4.4	210
Embarrassment minus neutral						
L visual cortex (cuneus, LG, FG)	−2	−89	4	17,18,19	4.91	4343
R visual cortex (cuneus, LG)	20	−70	0	17,18	5.52	
L MPFC (MFG, SFG)	−8	50	25	6,8,9,10	4.44	840
R MPFC (MFG, SFG)	2	59	17	9,10	3.75	
L posterior STS (MTG, STG)	−42	−59	18	39	4.24	185
L middle temporal cortex (MTG)	−51	−31	−7	21	4.56	132
L anterior temporal cortex (MTG)	−53	1	−24	21	4.3	50
R anterior temporal cortex (MTG, FG)	48	−7	−27	20	3.69	44
L OFC (IFG)	−44	31	−7	47	3.68	36
L hippocampus	−34	−18	−18		3.85	23

Coordinates and Z score refer to the peak of each brain region. BA = Brodmann area; L = left; R = right; LG = lingual gyrus; FG = fusiform gyrus; MFG = medial frontal gyrus; SFG = superior frontal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus; IFG = inferior frontal gyrus; MPFC = medial prefrontal cortex; STS = superior temporal sulcus; OFC = orbitofrontal cortex.

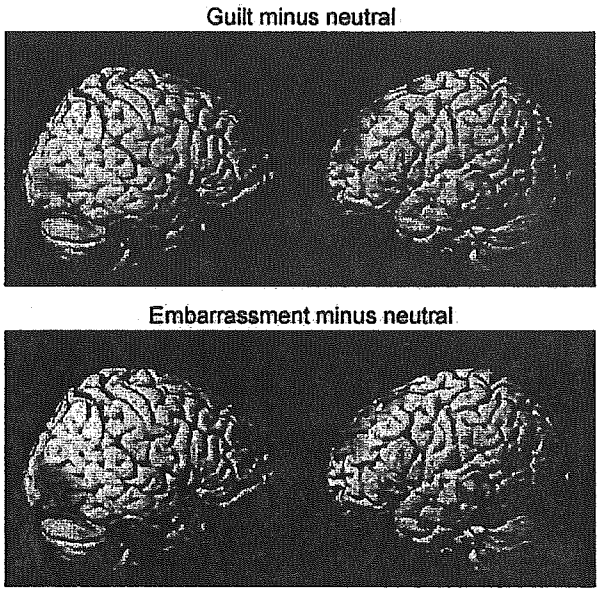

Fig. 2. Images showing brain activation in guilt and embarrassment conditions relative to neutral condition. Guilt minus neutral (top). Activated regions were in the MPFC, posterior STS, and visual cortex. Embarrassment minus neutral (bottom). In addition to activations in the MPFC, left posterior STS, and visual cortex, more widespread activations were shown in the left OFC, left temporal cortex (anterior and middle), and right temporal cortex (anterior). Note that both emotional conditions commonly activated the MPFC, left posterior STS, and visual cortex. Significant differences were recognized at a height threshold ($Z > 3.09$; $P < 0.001$, uncorrected) and extent threshold (15 voxels).

0.001, uncorrected) and extent threshold (15 voxels). We used a relatively large extent threshold to sufficiently minimize the risk of type 1 errors due to the relatively low height threshold. To assess common areas activated by the guilt and embarrassment conditions, we created a mask from the G − N contrast in the random effect analysis (threshold at $P < 0.001$, uncorrected). This mask was applied inclusively to the E − N contrast.

To ensure relative differences between activity associated with guilt and embarrassment, random effect analyses of guilt minus embarrassment contrast (G − E) and embarrassment minus guilt contrast (E − G) were conducted. Because one of the aims of this study was to investigate differences between guilt and embarrassment at the neural basis level, we reported the differences at a lower threshold (height threshold at $P < 0.005$, uncorrected, and extent threshold of 15 voxels).

We conducted additional analysis to demonstrate a more direct link between regional brain activity with subjective emotional judgments. Using the mean of ratings of guilt and embarrassment for each subject as the covariate, regression analyses with the contrast (G − N and E − N) and the covariate were done at the second level (height threshold at $P < 0.001$, uncorrected, and extent threshold of 15 voxels). Using the effect sizes, representing the percent signal change, of the contrasts (E − N and G − N) at the peak coordinates uncovered by regression analyses, we plotted fMRI signal changes and ratings of guilt and embarrassment. Coordinates of activation were converted from MNI coordinates to the Talairach and Tournoux (1988) coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA).

Results

Self-rating

The neutral sentences were judged as carrying neither guilty nor embarrassing contents. The mean ratings of guilt and embarrassment for neutral sentences were, respectively, 1.0 (SD = 0.0) and 1.0 (SD = 0.0), for guilt-related sentences 4.1 (SD = 0.7) and 1.6 (SD = 0.7), and for embarrassing sentences 1.5 (SD = 0.4) and 3.7 (SD = 0.6). The mean ratings of guilt were significantly greater for guilt-related sentences than for embarrassing sentences ($t = 10.6$, $df = 36$, $P < 0.001$). The mean ratings of embarrassment were significantly greater for embarrassing sentences than for guilt-related sentences ($t = 12.4$, $df = 36$, $P < 0.001$).

fMRI result

Guilt condition relative to neutral condition (G − N) produced greater activations in the MPFC, left posterior STS, and visual cortex. Embarrassment condition relative to neutral condition (E − N) produced greater activations in the MPFC, left posterior STS, left temporal cortex (anterior and middle), left orbitofrontal cortex (OFC), right temporal cortex (anterior), left hippocampus, and visual cortex (Table 2 and Fig. 2). In other words, both conditions commonly activated the MPFC, left posterior STS, and visual cortex (Table 3), but the embarrassment condition produced more widespread activations in the left temporal cortex (anterior and middle), right temporal cortex (anterior), left OFC, and left hippocampus.

Embarrassment condition relative to guilt condition (E − G) produced greater activation in the right temporal cortex (anterior), bilateral hippocampus, and visual cortex. In contrast, guilt condition relative to embarrassment condition (G − E) produced greater activation in the MPFC (Table 4 and Fig. 3).

Regression analyses revealed positive linear correlations between self-rating of guilt and the degree of activation in the

Table 3
Brain regions commonly activated by guilt and embarrassment conditions

Brain region	Coordinates			BA	*Z* score	Voxels
	x	*y*	*z*			
L visual cortex (LG)	−12	−77	6	17,18,19	4.37	1021
R visual cortex (LG)	2	−85	6	17,18	5.41	
L MPFC (MFG, SFG)	−10	36	52	8,9,10	4.35	429
R MPFC (MFG)	4	57	16	10	3.62	
L posterior STS (MTG)	−44	−61	20	39	4.4	101

A mask from the G − N contrast by random effect analysis (threshold at $P < 0.001$, uncorrected) was applied inclusively to the E − N contrast (height threshold at $P < 0.001$, uncorrected, and extent threshold of 15 voxels). See Table 2 legend.

Table 4
Comparisons between regional brain activities associated with guilt and embarrassment

Brain region	Coordinates			BA	Z score	Voxels
	x	y	z			
Embarrassment minus guilt						
R visual cortex (cuneus, LG, FG)	12	−83	8	17,18,19	3.28	393
R visual cortex (IOG)	38	−68	−5	19	3.59	49
L visual cortex (LG)	−10	−62	−2	18,19	3.48	140
L visual cortex (LG)	−8	−80	1	19	2.86	77
R anterior temporal cortex (MTG)	42	−3	−27	21	2.96	25
R hippocampus	32	−18	−13		2.91	32
L hippocampus	−20	−14	−9		3.21	49
Guilt minus embarrassment						
L MPFC (MFG)	−16	49	14	10	3.39	24

Random effect analyses of G − E and E − G contrast were conducted. See Table 2 legend.

MPFC (medial frontal gyrus, $x = -8$, $y = 55$, $z = 3$; $Z = 4.26$; 31 voxels), posterior STS (middle temporal gyrus, $x = -58$, $y = -56$, $z = 10$; $Z = 4.23$; 81 voxels), and visual cortex (lingual gyrus, $x = -14$, $y = -58$, $z = 3$; $Z = 3.82$; 24 voxels). There were positive linear correlations between self-rating of embarrassment and the degree of activation in the posterior STS (middle temporal gyrus, $x = -46$, $y = -57$, $z = 23$; $Z = 3.88$; 37 voxels) and visual cortex (lingual gyrus, $x = -16$, $y = -49$, $z = -4$; $Z = 3.48$; 20 voxels) (Figs. 4 and 5).

Discussion

We investigated the neural response associated with evaluative processes of self-conscious moral emotions. Recent neuroimaging studies have reported the neural substrate of moral judgment (Greene et al., 2001; Moll et al., 2002a,b). However, few reports are available on specific moral or social emotions (Berthoz et al., 2002; Shin et al., 2000). This study showed similarities and differences during evaluative processes of two moral emotions, guilt and embarrassment, at the neural basis level by measurements of neural responses in the same session.

As we predicted, both guilt and embarrassment conditions relative to neutral condition commonly produced greater activity in the components of neural substrates of social cognition or ToM, the MPFC, left posterior STS, along with the visual cortex. Several neuroimaging studies in healthy subjects using different variants of the ToM paradigm have consistently reported activation in the MPFC, predominantly on the left side (Fletcher et al., 1995; Gallagher et al., 2000; Goel et al., 1995). Additionally, autism, which is considered to have impairments in ToM, showed reduced activation in the MPFC (Baron-Cohen et al., 1999; Castelli et al., 2002; Happe et al., 1996). The MPFC has been suggested to play an important role in monitoring one's own mental state as well as that of others (Castelli et al., 2000; Frith, 2001). Recent studies reported that the MPFC was also recruited in moral judgment (Greene et al., 2001; Heekeren et al., 2003).

Activations in the posterior STS have also been consistently reported in social cognition or ToM tasks (Calder et al., 2002; Castelli et al., 2000; Gallagher et al., 2000; Winston et al., 2002) and in moral judgment tasks (Greene et al., 2001; Heekeren et al., 2003), while the area identical to the posterior STS was variously described as the temporoparietal junction or angular gyrus. Originally, STS was known to be activated by biological motions such as movement of eyes, mouth, hands, and body, but it has been suggested to have a more general function in social cognition (Adolphs, 2001; Allison et al., 2000), detection of intention (Gallagher et al., 2000), evaluation of trustworthiness of faces (Winston et al., 2002), detection of the behavior of agents and analysis of goal, and outcome of the behavior (Frith, 2001; Frith and Frith, 1999).

Common activations in the MPFC and posterior STS support the notion that both guilt and embarrassment are self-conscious

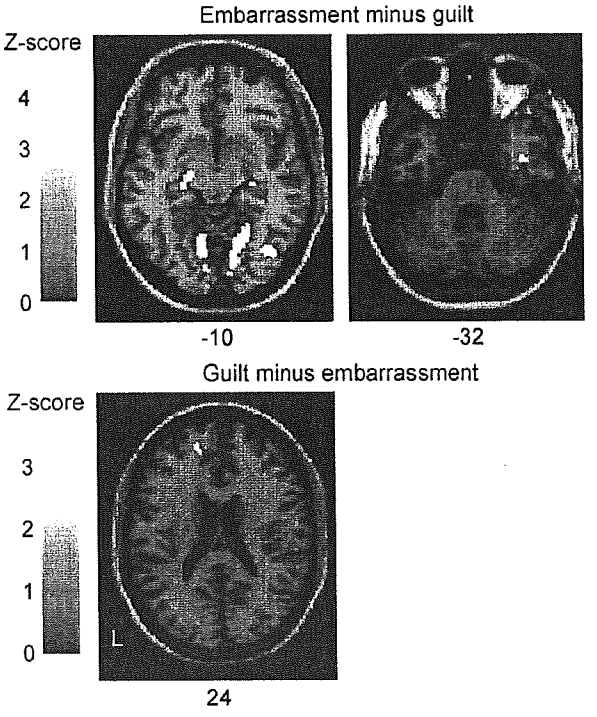

Fig. 3. Comparison of guilt and embarrassment conditions with height threshold ($P < 0.005$) and extent threshold (15 voxels). Embarrassment minus guilt (top). Compared to guilt, greater activation was shown in the right temporal cortex (anterior), bilateral hippocampus, and visual cortex. Guilt minus embarrassment (bottom). Compared to embarrassment, greater activation was shown in the MPFC. The bar shows the range of the Z score. Within the image, L indicates left. Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

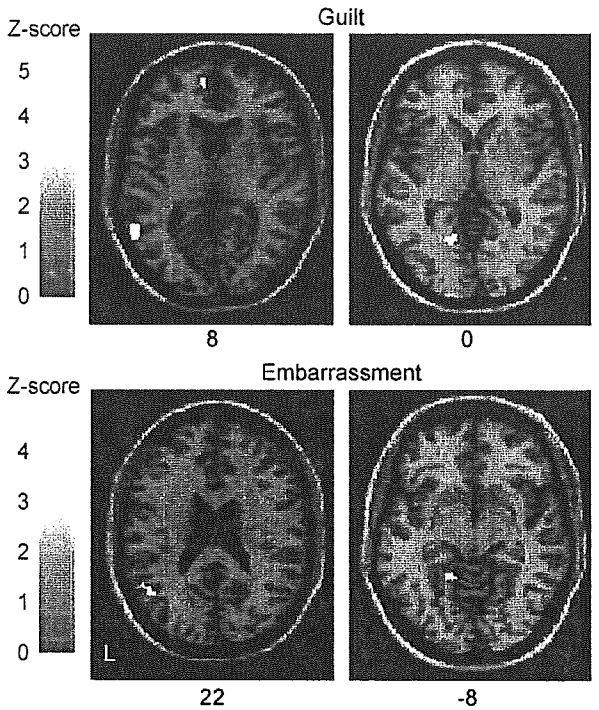

Fig. 4. Correlation between brain activation and the self-ratings of guilt and embarrassment with height threshold ($P < 0.005$) and extent threshold (15 voxels). There were positive linear correlations between self-rating of guilt and the degree of activation in the posterior STS and visual cortex (top). There were positive linear correlations between self-rating of embarrassment and the degree of activation in the posterior STS and visual cortex (bottom). The bar shows the range of the Z score. Within the image, L indicates left. Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

emotions that can arise from concerns about others' evaluation of one's own behavior (Eisenberg, 2000; Haidt, 2003; Tangney and Dearing, 2002). In other words, one needs the ability to take the perspective of others and to represent their mental state, that is, ToM, to understand the sense of guilt or embarrassment.

In spite of our attempt to control the linguistic features of the visual stimuli, increased activations were found in the visual cortex in response to the emotional conditions relative to the neutral condition. Enhanced visual cortex activations by emotionally salient visual stimuli have been extensively reported (Phan et al., 2002; Takahashi et al., 2004). Emotionally salient stimuli or attention demanding stimuli have been suggested as modulating sensory processing in the visual cortex. Early visual cortex receives prominent feedback projection from limbic structures such as amygdala (Emery and Amaral, 2000), and such pathway could act to enhance visual processing (Morris et al., 1998; Vuilleumier et al., 2001).

Interestingly, compared to the G – N contrast, the E – N contrast demonstrated more widespread activations in the left temporal cortex (anterior and middle), right temporal cortex (anterior), left OFC, and left hippocampus. Direct comparison between guilt and embarrassment conditions showed that the E – G contrast demonstrated significantly greater activation in the right anterior temporal cortex, bilateral hippocampus, and visual cortex. All these regions are also considered as the brain area related to social or moral cognition (Adolphs, 2001; Casebeer, 2003; Greene and Haidt, 2002; Moll et al., 2003). We did not expect the greater activation in the hippocampus in the embarrassment condition. The hippocampus is suggested to engage in retrieving behaviorally relevant memories (Strange et al., 1999). In moral judgment, the hippocampus might facilitate conscious recollection of memories that allow past events to affect current decisions (Casebeer, 2003).

Embarrassment has a higher affinity to the violation of social conventions (choices of clothing, etiquette and hygiene, etc.) that depend on societies or cultures, while guilt has a higher affinity to the violation of moral norms (issues of harm, right and justice, etc.) that are universal among human beings (Eisenberg, 2000; Haidt, 2003; Tangney et al., 1996). Moreover, embarrassment is uniquely a public emotion that depends on a real or imagined presence of others among one's self-conscious emotions. If people do experience embarrassment in private, it is a situation of vividly imagining what others might think of them (Miller, 1996; Tangney et al., 1996). Guilt does not necessarily depend on personal acquaintances. Guilt could be elicited not only by concerns with others' evaluation of self but also by private conscience (Haidt, 2003; Tangney and Dearing, 2002; Tangney et al., 1996). In light of these points, embarrassment could be regarded as a more social and public emotion that depends on personal interactions. Regression analyses showed that subjective ratings of guilt and embarrassment correlated with the degree of activation in the posterior STS, visual cortex, and MPFC, brain areas commonly activated by both emotional conditions. In other words, emotional intensity did not appear to account for the more widespread activation observed in embarrassment condition. Considering the regression analyses results, our interpretation was that the additional activations found in embarrassment condition might reflect more complex processes that detect and understand the complex social information of embarrassment.

This study has some limitations. First, a moral emotion could be accompanied by another emotion. For instance, guilt and shame could co-occur in some situations (Eisenberg, 2000). In moral transgression, people may feel guilty for violating a social norm and at the same time might feel shameful about one's own shortcomings. For this reason, we carefully chose the situations, although we understand that it is not feasible to extract "pure" emotion. Second, as mentioned above, embarrassment depends on society and culture. The social background of participants, such as gender, generation, religion, and education, could be confounding factors. Further studies that can control these factors would be recommended. Finally, we should acknowledge general limitations of a functional imaging study to reveal the neural substrates of social cognition or social emotions. The processing of social information is distributed in space and time, ranging from the perception of socially relevant stimuli to the elicitation of social behavior. Most functional imaging studies focused on the perception and interpretation of socially relevant stimuli. Emotional judgment tasks such as facial expression discrimination task or our task could also be regarded as a task of the perception and interpretation of socially relevant stimuli. It should be noted that emotional states that elicit social or emotional behaviors are not necessarily induced by merely viewing facial expressions or reading sentences. Social cognition is a domain with fuzzy boundaries and vaguely specified components. Processes of social cognition overlap with those of emotions. Although it is difficult to assess specific components of social cognition or emotions by a single modality, at least in this study, we assessed the evaluative processes of moral emotions. To complement fMRI studies, electrophysiological methods that have good temporal resolution

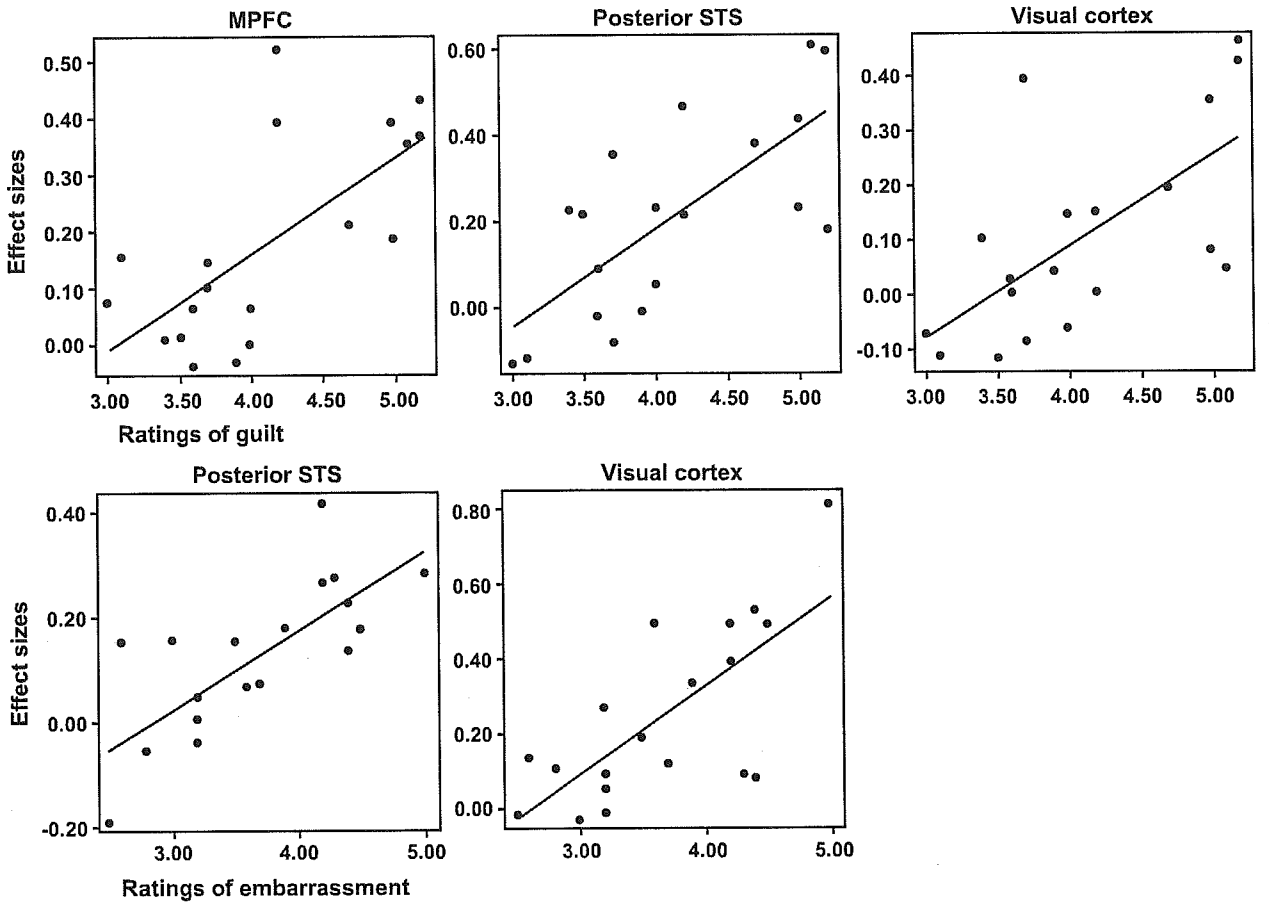

Fig. 5. Plots and regression lines of correlations between self-ratings and degree of activation in the brain regions. There were correlations between self-rating of guilt and degree of activation in the MPFC ($x = -8, y = 55, z = 3, r = 0.686, P < 0.005$), posterior STS ($x = -58, y = -56, z = 10, r = 0.722, P < 0.005$), and visual cortex ($x = -14, y = -58, z = 3, r = 0.653, P < 0.005$) (top). There were positive linear correlations between self-rating of embarrassment and degree of activation in the posterior STS ($x = -46, y = -57, z = 23, r = 0.744, P < 0.005$) and visual cortex ($x = -16, y = -49, z = -4, r = 0.719, P < 0.005$) (bottom).

would be recommended. Moreover, it is difficult to assess real-life human social behavior or to induce complex emotions in an MRI environment. Lesion studies can at least indicate the structures necessary for mediating social behavior (Adolphs, 2003).

Notwithstanding the difficulties in measuring social behavior, recording autonomic responses will be useful for assessing some aspects of social behavior or emotional responses. For instance, monitoring blushing, the hallmark of embarrassment, by recording face temperature or facial blood flow will be useful to distinguish embarrassment from guilt (Gerlach et al., 2003).

In conclusion, we investigated the neural substrates of evaluative processes of specific moral emotions and demonstrated similarities and differences between guilt and embarrassment at the neural basis level. Supporting the concept that both guilt and embarrassment could be regarded as self-conscious emotions, both emotional conditions produced similar activation patterns in the components of neural substrates implicated in social cognition or ToM. Moreover, our fMRI data lead us to conjecture that the evaluative process of embarrassment might be a more complex process than that of guilt. We expect our findings to contribute to a broadening of the knowledge concerning the neural basis of amoral behavior observed in neurological and psychiatric disorders.

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An fMRI study of differential neural response to affective pictures in schizophrenia

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Although emotional dysfunction is considered a fundamental symptom of schizophrenia, studies investigating the neural basis of emotional dysfunction in schizophrenia are few. Using functional magnetic resonance imaging (fMRI) and a task viewing affective pictures, we aimed to examine automatic emotional response and to elucidate the neural basis of impaired emotional processing in schizophrenia. Fifteen healthy volunteers and 15 schizophrenics were studied. During the scans, the subjects were instructed to indicate how each of the presented pictures made them feel. Whole brain activities in response to the affective pictures were measured by fMRI. Controls recruited the neural circuit including amygdaloid–hippocampal region, prefrontal cortex, thalamus, basal ganglia, cerebellum, midbrain, and visual cortex while viewing unpleasant pictures. Despite an equal behavioral result to controls, the patients showed less activation in the components of the circuit (right amygdala, bilateral hippocampal region, medial prefrontal cortex (MPFC), basal ganglia, thalamus, cerebellum, midbrain, and visual cortex). This study demonstrated functional abnormalities in the neural circuit of emotional processing in schizophrenia. In particular, decreased activation in the right amygdala and MPFC appears to be an important finding related to dysfunctional emotional behavior in schizophrenia.

Keywords: Schizophrenia; Emotion; Functional magnetic resonance imaging; Amygdala; Prefrontal cortex; Affective pictures

Introduction

Emotional dysfunction such as "flattening affect" or "anhedonia" is considered to be one of the key symptoms of schizophrenia (Andreasen and Flaum, 1991). Recent functional imaging techniques have revealed dysfunction of the neural circuit (interrelationship among cortical region, thalamus, basal ganglia, and cerebellum) in schizophrenia (Andreasen et al., 1999; Schultz and Andreasen, 1999). Most studies focused on cognitive dysfunction (Andreasen et al., 1999), while studies investigating the neural basis of dysfunctional emotional processing in schizophrenia are limited (Gur et al., 2002; Paradiso et al., 2003; Phillips et al., 1999; Schneider et al., 1998; Taylor et al., 2002). Previous neuroimaging studies in normal subjects revealed the neuroanatomical correlates of emotional processing and the crucial role of the amygdala in processing negative emotions. In particular, left-sided activations in the amygdala while processing negative facial expressions have been consistently reported (Calder et al., 2001). Recent functional magnetic resonance imaging (fMRI) studies revealed that schizophrenic patients demonstrated decreased activation in the bilateral amygdala during an emotion induction task by facial expressions (Schneider et al., 1998) or decreased activation in the left amygdala during a discrimination task of emotional facial expressions (Gur et al., 2002). However, discriminating analogous facial expressions is an effortful cognitive process whether subjects categorize the facial expressions by gender or emotion. Cognitive demands for elaborate recognition or detailed rating may modulate the emotional response in the brain (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Lange et al., 2003; Taylor et al., 2003). In addition, it should be noted that emotional facial expressions do not necessarily elicit the subjective experience of emotions (Davidson and Irwin, 1999).

Several activation studies used affective pictures to elicit emotion in healthy volunteers (Lane et al., 1997a,b). The task of simply viewing emotionally salient pictures could minimize cognitive demands and would be suitable for examining automatic emotional response. Only a few positron emission tomography (PET) studies have investigated the emotional processing of affective pictures with a task of rating subjective emotional experience (Taylor et al., 2002) or with a task of emotional

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perception (Paradiso et al., 2003) in schizophrenia, and these studies have not established consistent results for a better understanding of dysfunctional emotional processing in schizophrenia. To our knowledge, no fMRI study has examined the neural response across the whole brain to affective pictures in schizophrenia. In the present study, we used fMRI and a task with minimal cognitive demands to identify the neural circuit of automatic emotional processing. We expected the subjects to react to affective pictures without an effortful cognitive process and categorize them roughly according to their subjective emotional experiences. Comparing the neural responses of schizophrenic patients with those of healthy controls, we aimed to elucidate the neural basis of impaired emotional processing in schizophrenia.

Methods

Subjects

Fifteen schizophrenic patients (10 men and 5 women, mean age 29.0 years, SD = 6.9) meeting the DSM-IV criteria for schizophrenia were studied. Diagnoses were made by HT, YO, and the psychiatrists in charge based on a review of their charts and a conventionally semi-structured interview. Exclusion criteria were current or past substance abuse and a history of alcohol-related problems, mood disorder, or organic brain disease. Thirteen patients were recruited from the outpatient unit of Asai Hospital, and two were recruited from the inpatient unit. Eleven of the 15 patients received atypical neuroleptics (mean risperidone equivalent daily dosage = 1.60 mg, SD = 1.31), and the other four received no neuroleptics. The mean illness duration was 4.9 (SD = 4.9) years. Clinical symptoms were assessed by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The mean score of BPRS was 17.9 (SD = 5.7). The ratings were reviewed by HT and YO after the patient interview, and disagreements were resolved by consensus; consensus ratings were used in this study. Fifteen normal controls (nine men and six women, mean age 29.1 years, SD = 7.8) were recruited from the surrounding community. The candidates were carefully screened and standardized interviews were conducted by trained psychiatrists (HT and YO). They did not meet criteria for any psychiatric disorder. None of the controls were taking alcohol and 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. Patients had a tendency of a lower educational status (patients 13.7 ± 1.5 years, controls 14.9 ± 2.4 years; $P = 0.11$, t test). All of the patients and controls were right-handed, and they all underwent an MRI to rule out cerebral anatomic abnormalities. After the procedures had been fully explained to the subjects, written informed consent was obtained, as approved by the Ethics Committee.

Stimulus and self-rating

Stimulus materials were taken from the International Affective Picture System (IAPS) (Lang et al., 1997). Pictures were divided into three emotional classes (neutral, unpleasant, and pleasant) according to the subjective ratings provided by IAPS. We employed 40 pictures from each class. The mean valence and arousal ratings of 40 pictures were 5.87 (SD = 0.77) and 3.75 (SD = 1.11) for neutral, 3.07 (SD = 0.69) and 5.75 (SD = 0.83) for unpleasant, and 7.42 (SD = 0.36) and 4.65 (SD = 0.95) for pleasant pictures. Slides of the three emotional classes were matched for content (faces, human figures, animals, objects, and scenery). The pictures were projected via a computer and a telephoto lens onto a screen with a mirror mounted on a head-coil. The experimental design consisted of eight blocks for each of the three conditions (neutral, unpleasant, and pleasant) interleaved with 20-s rest periods. During the rest condition, subjects viewed a crosshair projected at the center of the screen. In each 20-s block, five different pictures of the same emotional class were presented for 3.5 s each, with an interstimulus interval of 0.5 s. During the scans, the subjects were instructed to indicate how each picture made them feel by categorizing their subjective emotions into three emotional classes (neutral, unpleasant, and pleasant) using buttons. Signals from the buttons were transmitted to a computer outside the shielded room via infrared rays to confirm whether expected emotions were evoked in response to individual affective pictures. The rate of the appearance of expected categorizations from the 40 pictures of the same emotional class was calculated for each emotional condition. We compared the percentages of expected categorizations between the patient and control groups.

fMRI acquisition

The images were acquired with a 1.5-T Signa system (General Electric, Milwaukee, WI). Functional images of 240 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).

Analysis of functional imaging data

Data analysis was performed with statistical parametric mapping software package (SPM99) (Wellcome Department of Cognitive Neurology, London, UK) that runs 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 (MNI) 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 (cut-off period = 240 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. These images were scaled to give a grand mean signal of 100 across all voxels in all images to remove global effects. 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. The t values were then transformed to unit normal distribution, resulting in z scores.

We assessed the neutral vs. rest, the unpleasant vs. rest, and the pleasant vs. rest contrasts. To assess the specific condition effect, we used the contrasts by subtracting the neutral condition from the pleasant condition and the unpleasant condition. 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 to the population from which data are obtained. The contrast images were obtained from single-subject analysis and were entered into the group analysis. A one-sample t test was applied to determine group activation for each effect. Significant clusters of activation were determined using the conjoint expected probability distribution of the height and extent of z scores with the height and extent threshold. In addition, we tested for relative differences in the pattern of neural activation by

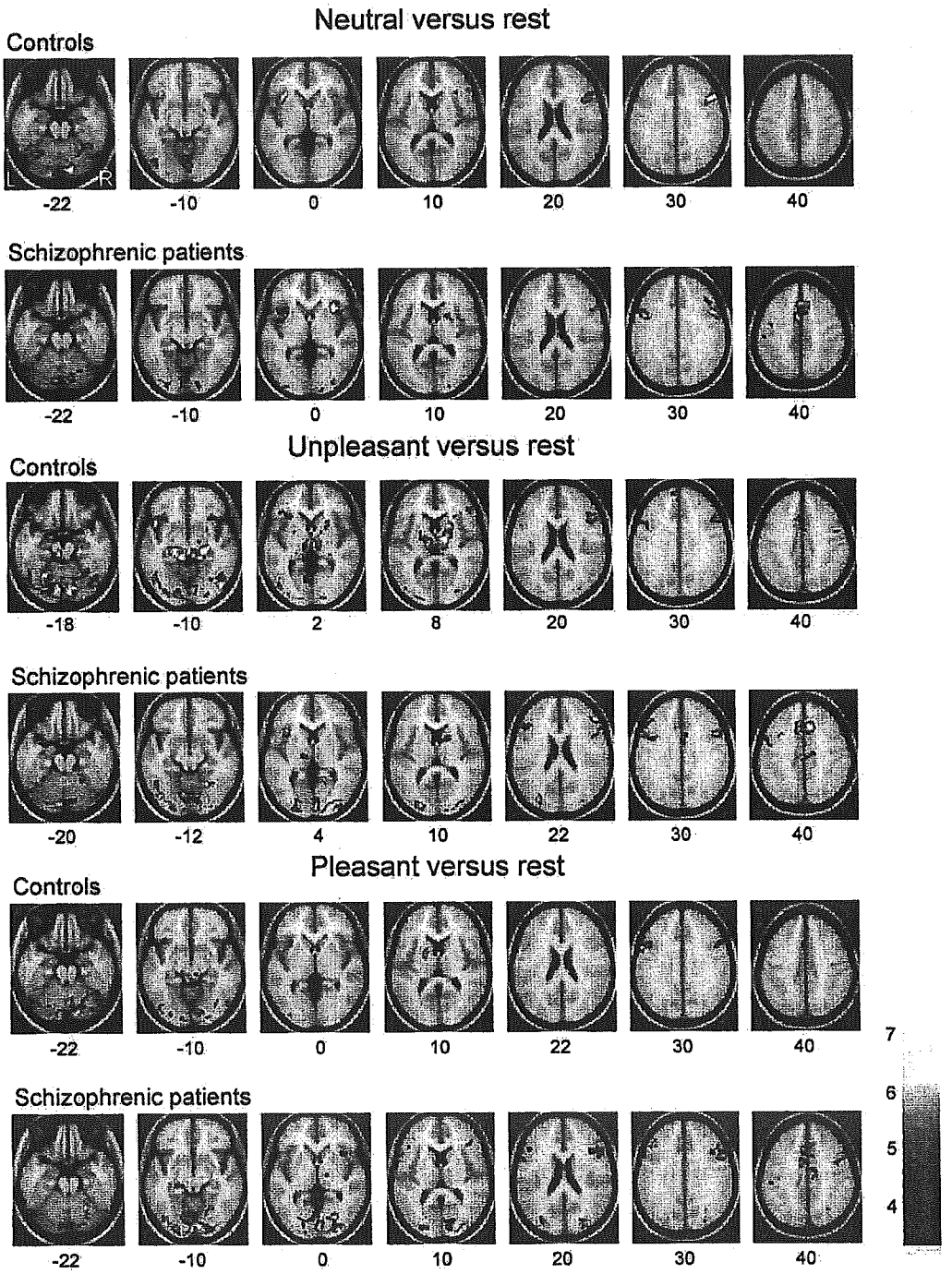

Fig. 1. Images showing brain regions of significant activation during the neutral and unpleasant conditions relative to the rest condition in 15 controls and 15 schizophrenic patients. The bar shows the range of the z score. Within the image, L indicates left and R indicates right. Significant differences were accepted at a height threshold ($z > 4.75$; $P < 0.000001$, uncorrected) and extent threshold (30 voxels). Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

Table 1
Brain regions of significant activation during unpleasant condition relative to neutral in 15 controls and 15 schizophrenic patients

	Brain region	Brodmann's area	Coordinates[a]			z score[b]
			x	y	z	
Controls	Left lingual gyrus	17, 18, 19	−16	−88	−9	5.61
	Right lingual gyrus	17, 18, 19	8	−82	−1	5.33
	Left fusiform gyrus	19, 37	−32	−76	−8	5.8
	Right fusiform gyrus	18, 37	22	−88	−11	4.95
	Posterior cingulate	31	−2	−53	23	4.39
	Left hippocampal region	34, 35	−18	−26	−12	5.31
	Right hippocampal region	27, 28	24	−24	−9	5.55
	Left amygdala		−24	−3	−18	4.29
	Right amygdala		28	−1	−18	5.02
	Left thalamus		−10	0	7	4.71
	Right thalamus		18	−8	10	4.18
	Left caudate nucleus		−14	10	11	4.7
	Medial prefrontal cortex	9	−4	50	25	4.73
	Right orbitofrontal cortex	47	32	27	−6	4.65
	Cerebellum		32	−77	−18	6.18
	Midbrain		−6	−33	−8	5.35
Schizophrenia	Left lingual gyrus	17, 18, 19	−18	91	3	4.68
	Right lingual gyrus	17	14	−90	6	4.07
	Left fusiform gyrus	19	−20	−80	−11	4.3
	Right fusiform gyrus	19	24	−80	−11	4.33[c]
	Left amygdala		−22	−6	−18	4.56[c]

[a] Talairach and Tournoux coordinates in the local point of maximal activation included in the cluster.
[b] Significant differences were accepted at a height threshold ($z > 3.89$; $P < 0.00005$, uncorrected) and extent threshold (30 voxels).
[c] Right visual cortex and left amygdala in schizophrenia survived the height threshold but not the extent threshold.

subtracting the unpleasant minus neutral (U − N) contrasts of the patients from the U − N contrasts of the controls and vice versa. Between-group comparison was performed with a two-sample *t* test. Using the effect sizes, representing the percent signal change, of the U − N contrasts at the regional maxima uncovered in the between-group comparisons, we analyzed whether the BOLD signal change was correlated with the dosage of neuroleptics and the BPRS score. Coordinates of activation were converted from MNI coordinates to Talairach and Tournoux (1988) coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA). Contrast images were overlaid onto a group mean anatomy image provided by SPM for viewing.

Results

Self-rating

The mean percentages of expected categorizations of the controls for the neutral, unpleasant, and pleasant pictures were 85.3% (SD = 8.3), 88.8% (SD = 11.3), and 59.0% (SD = 22.8), respectively, and those of the schizophrenic patients were 81.3% (SD = 8.3), 92.0% (SD = 9.5), and 55.0% (SD = 34.8), respectively. Two-way repeated-measures analysis of variance of the percentages of expected categorizations showed a significant main effect of condition ($F = 27.6$, $df = 2, 84$, $P < 0.001$), but not a significant main effect of group ($F = 0.26$, $df = 1, 84$, $P = 0.61$) or interaction ($F = 0.44$, $df = 2, 84$, $P = 0.64$). A post hoc test revealed that the percentage of expected category for the pleasant pictures was lower than those for the neutral and unpleasant pictures. That is, the subjects did not categorize the pleasant pictures as we had expected. Most of the remaining pictures not regarded as pleasant were categorized as neutral.

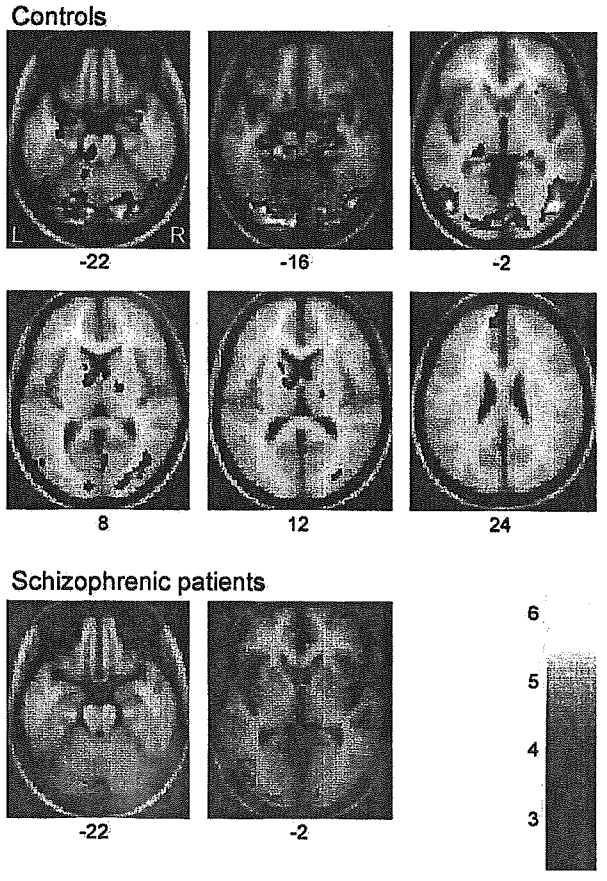

Fig. 2. Images showing brain regions of significant activation during unpleasant condition relative to neutral in 15 controls and 15 schizophrenic patients. The bar shows the range of the *z* score. Within the image, L indicates left and R indicates right. Significant differences were accepted at a height threshold ($z > 3.89$; $P < 0.00005$, uncorrected) and extent threshold (30 voxels). (Right visual cortex and left amygdala in the schizophrenic patients survived the height threshold but not the extent threshold.) Numbers in the bottom row indicate the *z* coordinates of the Montreal Neurological Institute brain.

fMRI data

Within-group comparisons

Both groups showed similar activation patterns in the neutral vs. rest contrast and in the pleasant vs. rest contrast (Fig. 1, top and bottom). Moreover, activation patterns in the neutral vs. rest contrast and the pleasant vs. rest contrast were also similar. In fact, significant activation in response to pleasant pictures relative to neutral pictures was seen only in the visual cortex (lingual gyrus) across groups (height threshold: $z > 4.75$ and extent threshold > 30 voxels). However, the two groups showed different activation patterns during the unpleasant condition compared to the rest condition (Fig. 1, middle). The controls demonstrated significant activation in response to unpleasant pictures relative to neutral pictures in the bilateral primary and secondary visual cortex, bilateral amygdala, bilateral hippocampal regions, medial prefrontal cortex (MPFC), right orbitofrontal cortex (OFC), bilateral thalamus, left caudate nucleus, cerebellum, and midbrain. Patients demonstrated significant activation in response to unpleasant pictures relative to neutral pictures in the bilateral primary and secondary visual cortex and left amygdala (Table 1 and Fig. 2).

Between-group comparisons

The group comparison of the U − N contrasts showed that schizophrenic patients demonstrated less activation in the right amygdala, bilateral hippocampal regions, MPFC, left visual cortex, left putamen, left caudate nucleus, left posterior thalamus, cerebellum, and midbrain (Table 2 and Fig. 3). No significantly greater activation was identified in schizophrenic patients in the between-group comparison of the U − N contrasts. We did not use between-group analysis for the pleasant minus neutral (P − N) contrast due to its meager activation across groups, possibly resulting from insufficient elicitation of pleasantness.

Correlations with BOLD signal change

There were no correlations between dosage of neuroleptics and signal change in the brain regions where patients showed decreased activation. In addition, no correlations were found between the BPRS score and signal change in these regions (Pearson's correlation analysis, $P > 0.05$).

Table 2
Brain regions with relatively less activation (unpleasant minus neutral) in 15 schizophrenic patients compared with 15 normal controls

Brain region	Brodmann's area	Coordinates[a]			z score[b]
		x	y	z	
Left lingual gyrus	18	−8	−88	−11	3.18
Left hippocampal region	30, 35	−14	−32	−12	3.83
Right hippocampal region	28	26	−24	−9	3.14
Right amygdala		24	−3	−13	3.39
Left thalamus		−22	−25	1	3.08
Left putamen		−20	12	9	2.88
Left caudate nucleus		−16	14	14	2.87
Medial prefrontal cortex	9	−2	54	25	3.21
Cerebellum		−14	−46	−23	3.06
Midbrain		−6	−26	−10	3.15

[a] Talairach and Tournoux coordinates in the local point maximal activation included in the cluster.

[b] Activation differences were considered significant at height threshold ($z > 2.57$; $P < 0.005$, uncorrected) and extent threshold (30 voxels).

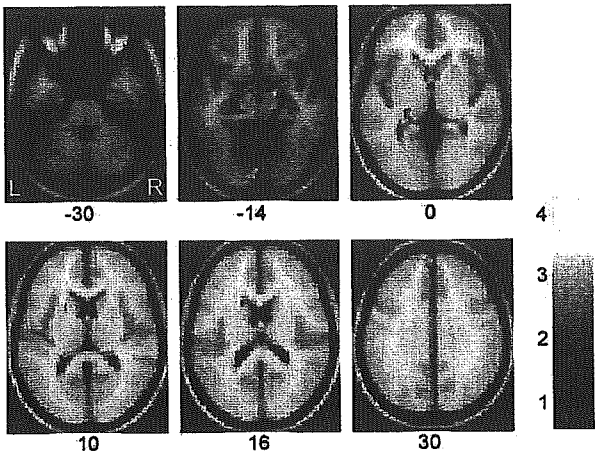

Fig. 3. Images showing brain area of relatively less activation (unpleasant minus neutral) in 15 schizophrenic patients compared with 15 normal controls. The bar shows the range of the z score. Within the image, L indicates left and R indicates right. Activation differences were considered significant at height threshold ($z > 2.57$; $P < 0.005$, uncorrected) and extent threshold (30 voxels). Numbers in the bottom row indicate the z coordinates of the Montreal Neurological Institute brain.

Discussion

In control subjects, we identified the neural circuit of the automatic emotional response to unpleasant pictures in the amygdaloid–hippocampal region, thalamus, OFC, MPFC, basal ganglia, cerebellum, midbrain, and visual cortex. We used evocative pictures with minimal cognitive demands so as to examine the automatic emotional response that requires no elaborate rating or categorization of stimuli for the subjects. Facial expressions do not necessarily elicit strong emotions, and cognitive demands such as discriminating analogous facial expressions might affect brain activations (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Lange et al., 2003; Taylor et al., 2003). Passive emotional tasks with minimal cognitive demands might activate the amygdala and other subcortical regions more often than emotional tasks with greater cognitive demands (Phan et al., 2002). Thus, we successfully observed robust activation in widespread cortical and subcortical regions as reported in previous studies (Lane et al., 1997a,b).

The cortical–basal ganglia–thalamic circuit has been implicated in cognitive or emotional processing (Alexander et al., 1986). The circuit involving the components of the cortical–basal ganglia–thalamic circuit along with the amygdala appears to be involved in the control of emotional behavior (Groenewegen and Uylings, 2000; Price et al., 1996), and dysfunction of this circuit is considered to cause mood disorder (Drevets, 2001).

Despite similar categorizations of pictures for the controls, patients demonstrated less activation in the amygdaloid–hippocampal region, MPFC, thalamus, basal ganglia, cerebellum, midbrain, and visual cortex. This finding represented evidence of functional abnormalities in the neural circuit involving the cortical–basal ganglia–thalamic circuit and the amygdala in schizophrenia. Our patients showed decreased cerebellar activation as well. Considering the fact that neuroimaging studies of schizophrenia using a variety of cognitive tasks have demonstrated a disruption in the cortical–cerebellar–thalamic–cortical circuit

(CCTCC) leading to cognitive deficits (Andreasen et al., 1999), the functional abnormalities in the CCTCC along with the limbic area might lead to the emotional dysfunction in schizophrenia. Our results could also be interpreted in this manner, supporting the notion that schizophrenic patients have disruption in the distributed neural circuit, although cortical regions vary depending on the task (Andreasen et al., 1999).

The amygdala and PFC are considered to be key nodes of the neural circuit of emotional processing, the former a main signal generator and the latter a modulator (Davidson, 2002; Drevets, 2000). Previous fMRI studies using facial expressions showed decreased activation in the bilateral amygdala (Schneider et al., 1998) or left amygdala (Gur et al., 2002) in schizophrenia. However, our patients showed significantly less activation in the right amygdala. These inconsistent findings might be due to differences in the emotional tasks. The left amygdala activation has been consistently reported in the processing of emotional facial expressions (Calder et al., 2001), and the right amygdala has been suggested to have a higher affinity with picture processing (Keightley et al., 2003; Markowitsch, 1998). It has also been suggested that cognitive or attention-demanding aspects of the emotional task could attenuate amygdala activation (Critchley et al., 2000; Hariri et al., 2000; Keightley et al., 2003; Taylor et al., 2003). Using affective pictures and minimizing cognitive demands, we demonstrated robust activation in the right amygdala as well as in the left amygdala in controls. This result concerning right amygdala activation could be attributed to group differences. Another interpretation of patients showing less activation in the right amygdala might be possible. Several lines of evidence have suggested the functional laterality of the amygdala, that is, the right amygdala may engage in a rapid automatic processing of ambiguous information, while the left amygdala may participate in conscious evaluation of significant stimuli (Critchley et al., 2000; Markowitsch, 1998; Morris et al., 1998, 1999; Phelps et al., 2001; Wright et al., 2001). Taking this into account, schizophrenic patients might have relatively intact function of conscious processing of significant information, leading to a categorization of pictures similar to that of controls, but impairment of the rapid, automatic processing of salient stimuli. In other words, patients could assign significance to stimuli through conscious processing, but they might have diminished automatic emotional response to external stimuli.

A PET study using IAPS reported that schizophrenic patients showed decreased activation in the right amygdala in response to non-aversive pictures (Taylor et al., 2002). In that study, non-aversive pictures elicited robust activation in the bilateral amygdala and aversive pictures failed to elicit greater activation in the amygdala relative to non-aversive pictures. In other words, their non-aversive pictures were not "neutral" and they might have contained emotionally salient features. In this regard, our result is consistent with this previous finding. By contrast, another recent PET study using IAPS reported decreased activation in the left amygdala in schizophrenia (Paradiso et al., 2003). Unfortunately, the study did not set up a neutral condition. Without such a condition, it remains unclear whether the decreased activation in response to unpleasant pictures stems from impairment in emotional processing of unpleasant pictures or in a more basic cognitive function such as visual perception or object recognition. We ruled out the latter possibility by comparing the activation in response to neutral stimuli across groups. Obviously, more research is needed on the abnormal amygdala function in schizophrenia.

Within the PFC, another key node of the neural circuit of emotional processing, we found decreased activation in the MPFC in patients. The MPFC was commonly activated in studies about emotional response in healthy subjects, and its activation was not specific to particular emotion or induction methods with or without cognitive components (Phan et al., 2002). The MPFC is assumed to play general roles in emotional processing such as attention to emotion, identification or regulation of emotion (Reiman et al., 1997; Teasdale et al., 1999), and guiding motivational behavior by modulating or appraising autonomic emotional responses (Drevets, 2001; Epstein et al., 1999; Phillips et al., 2003). The decreased activation in the MPFC in our patients appears to be an important finding with respect to abnormal motivational behavior in schizophrenia. In contrast, the PET study using IAPS showed hyperactivation in the MPFC in schizophrenia, contrary to the author's expectation (Taylor et al., 2002). These contradictory results therefore emphasize the need for further studies of the activation of the MPFC in schizophrenia.

The present study has several limitations. First, most of the patients were taking neuroleptic medications, possibly affecting neural activation. They were, however, taking atypical neuroleptics, and at relatively low doses. To our knowledge, there has been no previous study on the effect of neuroleptics on the BOLD response of emotional processing. Compared to typical neuroleptics, atypical neuroleptics have shown less influence on BOLD contrast in the motor area or thalamus during a finger-tapping task (Braus et al., 1999; Muller and Klein, 2000). Future studies with neuroleptic-naive patients, where the effect of neuroleptics can be controlled, will clarify this possible limitation. Second, we could not demonstrate any correlation between signal changes and BPRS scores in patients, possibly due to a lack of dispersion in the psychopathology of the patients, most of them being non-deficit outpatients with mild psychiatric symptoms. Third, the unpleasant pictures contained emotional features ranging from fear to disgust, and we could not differentiate the processing of particular emotions. In the processing of fear, the amygdala plays a central role. In contrast, the basal ganglia rather than the amygdala is considered to be essential in the processing of disgust (Calder et al., 2001; Phan et al., 2002). Thus, activation in the components of the neural circuit, the amygdala and basal ganglia, might reflect both emotional processing. Finally, we have difficulties in measuring emotional behaviors. This point has implications for the interpretation of the discrepancy between normal behavioral result and the abnormal neural activations observed in schizophrenic patients, as was also reported in previous studies (Gur et al., 2002; Paradiso et al., 2003; Schneider et al., 1998; Taylor et al., 2002). Our task could be regarded as an emotion-induction task. However, the finding needs to be interpreted cautiously because, strictly speaking, our task was testing the access to autonoetic perception of elicited emotions. It might be possible that the ability of schizophrenic patients to access their emotions (categorization of feeling) was different from that of normal controls. Our behavioral results might not necessarily reflect gut-level elicited emotion that drives emotional behavior. Autonomic data such as skin conductance responses would help to measure gut-level emotional response.

In conclusion, we investigated the automatic emotional response in healthy controls and schizophrenic patients. By using a task with minimal cognitive demands, we identified robust activation across the neural circuit of emotional processing including the amygdaloid–hippocampal region, prefrontal cortex, thalamus, and basal ganglia in response to unpleasant stimuli in the controls.

Schizophrenic patients demonstrated less activation in the components of the circuit. In particular, decreased activation in the right amygdala and MPFC, the key structures in the circuit, could be related, respectively, to diminished automatic emotional response to external stimuli and impairment in regulating emotional responses to guide emotional behavior in schizophrenia.

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Regular Article

Neural damage due to temporal lobe epilepsy: Dual-nuclei (proton and phosphorus) magnetic resonance spectroscopy study

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Abstract The aim of this study was to evaluate the usefulness of proton and phosphorus (^{1}H and ^{31}P) magnetic resonance spectroscopy (MRS) for temporal lobe epilepsy (TLE) patients, and to evaluate neural damage and metabolite dysfunction in the TLE patient brain. We performed ^{1}H and ^{31}P MRS of medial temporal lobes (MTL) in the same TLE patients ($n = 14$) with a relatively wide range of severity from almost seizure-free to intractable, and calculated the ratio of N-acetylasparate to choline-containing compounds and creatine + phosphocreatine (NAA/Cho + Cr) in ^{1}H MRS and inorganic phosphate to all main peaks (%Pi) in ^{31}P MRS. There was no significant correlation between NAA/(Cho + Cr) and %Pi in each side (ipsilateral, $r = -0.20$; contralateral, $r = -0.19$). The values of NAA/(Cho + Cr) showed a significant difference between ipsilateral and contralateral MTLs to the focus of TLE patients ($P < 0.01$, paired t-test). Although %Pi also had a tendency to show the laterality of TLE, there was no significance. Ipsilateral ($r = -0.90$, $P < 0.0001$) and contralateral ($r = -0.70$, $P < 0.005$) NAA/(Cho + Cr) decreases and contralateral %Pi increase ($r = 0.81$, $P < 0.001$) had significant correlation with seizure frequency. ^{1}H MRS provides more important information concerning neuronal dysfunction in MTL of TLE patients than ^{31}P MRS.

Key words lateralization, medial temporal sclerosis, proton and phosphorus magnetic resonance spectroscopy, temporal lobe epilepsy.

INTRODUCTION

Surgical treatment for medically intractable temporal lobe epilepsy (TLE) is an effective procedure in selected patients in whom the epileptogenic focus is localized in a unilateral anterior and medial temporal lobe (MTL).[1] Accurate localization of the epileptogenic focus has largely and traditionally been dependent on a scalp-sphenoidal electroencephalogram (EEG). Recently, magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) have provided important additional information about the epileptogenic focus.[2,3] However, subdural EEG electrode implantation is still required when imaging and scalp EEG are inconclusive. Thus, a more sensitive and non-invasive neurological measurement modality is needed that interictally lateralizes the epileptogenic focus and provides useful information about the pathological changes of TLE.

Magnetic resonance spectroscopy (MRS) is widely used in the field of psychiatry and clinical neuroscience.[4–17] Proton and phosphorus magnetic resonance

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spectroscopies (^{1}H and ^{31}P MRS) were non-invasive functional neurological measurement modalities. Proton MRS of the brain includes signals from N-acetylasparate (NAA), choline-containing compounds (Cho) and creatine + phosphocreatine (Cr). There have been several studies that observed a reduction in the NAA signal or its ratio to other metabolic signals in the ipsilateral temporal lobe to the epileptogenic focus in TLE patients, suggesting that NAA concentration reflects neural damage.[4–13] The values of inorganic phosphate (Pi) and phosphocreatine (PCr) that can be detected in ^{31}P MRS change according to the condition of oxidative phosphorylation, and they were reported to be good indexes for detecting brain metabolite dysfunction.[14–16]

Magnetic resonance nuclei have been used in TLE studies, but studies using both nuclei MRS of the same TLE patients have hardly been reported. In the present study, we aimed to evaluate the ^{1}H and ^{31}P MRS signal changes in bilateral temporal lobes of TLE patients with a relatively wide range of severity from almost seizure-free to intractable, and to clarify the relation between neural damage and metabolite dysfunction in the TLE patient brain. Some ^{1}H MRS data in this study was from that already reported by Someya *et al.*[11]

METHODS

Subjects

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. We studied 14 patients, four males and 10 females, aged 31.5 ± 8.4 years (mean ± SD), who were diagnosed with the amygdala-hippocampus type of TLE on the basis of clinical symptoms and EEG findings.[18] They were asked to participate in this study, and written informed consent was obtained. The patients showed unilateral temporal spikes or sharp waves in their repetitive (three or more) scalp EEG and/or stereotactic implanted depth electrode EEG record. The data of the patients are summarized in Table 1. Seven healthy volunteers, five males and two females, aged 27.0 ± 5.4 year (mean ± SD), were also studied as controls. No significant difference was observed in gender ($P = 0.06$; Pearson's χ^2 test) or age ($t = 1.37$, $P = 0.19$; t-test) between controls and patients.

Table 1. Patient demographic information

Subject	Sex	Age	Drug (mg)	Onset age (y)	Epilepsy duration (y)	EEG focus	Seizure type per month	Seizure frequency	MRI
1	F	20	DPH 225, CBZ 800, ZNS 200	15	5	Left	SPS + CPS	<1	Atrophy of Lt-MTL
2	F	22	CBZ 300, DPH 100	20	2	Left	SPS + CPS	<1	(–)
3	F	27	CZP 4, ZNS 400, VPA 1000	2	25	Left	CPS	<1	Atrophy of Lt-MTL
4	F	30	CBZ 600, ZNS 500	10	20	Left	SPS + CPS	<1	(–)
5	M	22	DPH 200	14	8	Left	SPS + CPS	<1	(–)
6	M	30	CBZ 400	26	4	Right	CPS	<1	(–)
7	F	20	ZNS 200, CBZ 800, DPH 100	15	5	Left†	SPS + CPS	18.3	(–)
8	F	34	CBZ 800, ZNS 400	10	24	Left	CPS+SGS	8.5	(–)
9	F	37	PB 50, CBZ 1200, DPH 350	18	19	Right†	SPS + CPS+SGS	33.3	(–)
10	F	37	CBZ 800, ZNS 400	9	28	Left	SPS + CPS+SGS	3.0	(–)
11	F	40	CBZ 800, ZNS 200	15	25	Left	CPS+SGS	2.6	(–)
12	F	47	CBZ 1000, VPA 600	20	27	Left	SPS + CPS+SGS	3.6	Atrophy of Lt-MTL
13	M	36	VPA 600	6	30	Right	CPS	9.5	Atrophy of Rt-MTL
14	M	39	DPH 450, CBZ 800, VPA 1600	3	36	Right	CPS+SGS	8.8	(–)

CBZ, carbamazepine; CZP, clonazepam; DPH, diphenylhydantoin; PB, phenobarbital; VPA, valproate sodium; ZNS, zonisamide; SPS, simple partial seizure; CPS, complex partial seizure; SGS, secondarily generalized seizure; MTL, medial temporal lobe.

†Results by stereotactic implanted depth electrode EEG.

Magnetic resonance spectroscopy

The MR system used in this study was a Gyroscan ACS2 operated at 1.5T (Philips Medical Systems Ltd, Best, The Netherlands). ^{1}H and ^{31}P MRS were performed with a birdcage-type coil. The volumes of interest (VOIs) were set at the bilateral MTL under the guidance of proton scout images, with their size being $6 \times 3 \times 3$ cm so as to include all parts of the hippocampus: the head, body, tail, gray and white matter, and amygdala. For ^{1}H MRS, volume selection was done by spin echo sequence for each side. Repetition time (TR) was 1500 msec. The echo time (TE) used was 136 msec because lactate peaks are visible at this TE. There were 1024 data points, and the bandwidth was 2000 Hz. Scan averages were 256 times and scan time was 6.4 min for each side. For ^{31}P MRS, the volume selection was done by two-VOI image-selected *in vivo* spectroscopy (2-VOI ISIS) sequence. TR was 3000 msec. Data points were 1024 and the bandwidth was 2000 Hz. The scan time was 20 min (384 scans).

To evaluate the structural brain changes, approximately 90 coronal MR images, covering the entire brain, were taken for each subject. An inversion recovery pulse sequence (TR, 2500 msec; TE, 20 msec; inversion time, 300 msec) was used. Matrix size was 205×256, and the FOV was 230 mm. Slice thickness was 2 mm without slice gaps. Total scan time was 21 min and 25 s. The coronal slice images were parallel to the baseline of the fourth ventricle. Atrophy of the MTL was judged by two experienced specialists, a radiolologist and a neuropsychiatrist, while were blind to the EEG lateralization.

Data processing and analysis

The spectra in ^{31}P MRS were processed with a 15-Hz exponential filter in the time domain. No filter was used in ^{1}H MRS. To measure the area under each peak, a semi-automatic line-fitting routine assuming a purely Lorentzian line shape was used. NAA intensities were evaluated as relative ratio to the total ratio of Cho and Cr. The Pi value was shown as relative value to the total value of all the peaks (phosphoesters, Pi, phosphocreatine, and adenosine triphosphate).

The paired *t*-test was used for comparisons of ipsilateral and contralateral MTL to the EEG focus, and the unpaired *t*-test was used for comparisons of control and patient MTL. Logarithmic transformation was used to normalize the data of seizure frequency. Pearson product-moment correlation analysis was used to evaluate the correlation between each set of MRS data and seizure frequency. Differences were considered to be significant at $P < 0.05$.

RESULTS

There was no significant correlation between NAA/(Cho + Cr) and %Pi on each side (ipsilateral $r = -0.20$; contralateral $r = -0.19$). Atrophy of MTL was detected by MRI in four patients (Table 1). Their lateralities were consistent with the EEG and MRS lateralities except for one case that had lower %Pi in the ipsilateral MTL.

Proton MRS

Proton MRS lateralization based on a reduced NAA/(Cho + Cr) ratio was in agreement with the clinical EEG lateralization in 12 of 14 patients, and a significant difference between the ipsilateral and contralateral MTL ($P < 0.01$, paired *t*-test) (Table 2) was obtained. The NAA/(Cho + Cr) ratio in the ipsilateral or contralateral MTL was not significantly different from that in MTL of control subjects. Two cases with disagreement between the results of ^{1}H MRS and clinical data were in the low seizure-frequency group (< 1/month).

NAA/(Cho + Cr) in the ipsilateral and contralateral MTL decreased as the seizure frequency increased. Both ipsilateral and contralateral NAA/(Cho + Cr) were significantly correlated with seizure frequency ($r = -0.90$, $P < 0.0001$; $r = -0.70$, $P < 0.005$, respectively; Fig. 1a).

Phosphorus MRS

Phosphorus MRS lateralization based on an increase in %Pi ratio was consistent with the clinical EEG lateralization in 10 of 14 patients, but there was no significant difference (Table 2). The %Pi value in the ipsilateral or contralateral MTL was not significantly different from that in MTL of control subjects. In 10 of 14 patients, the %Pi values in the ipsilateral MTL were higher than the mean value of normal control. They were very scattered, and had no significant correlation

Table 2. Relative signal intensity of proton and phosphorus MRS

	Control	Ipsilateral	Contralateral
%NAA/(Cho + Cr)	82 ± 7	72 ± 9*	79 ± 7*
%Pi	5.0 ± 1.4	5.8 ± 1.4	4.9 ± 1.3

Values are mean ± SD.

NAA, N-acetylasparate; Cho, choline-containing compounds; Cr, creatine + phosphocreatine; Pi, inorganic phosphate.

*$P < 0.01$, paired *t*-test.

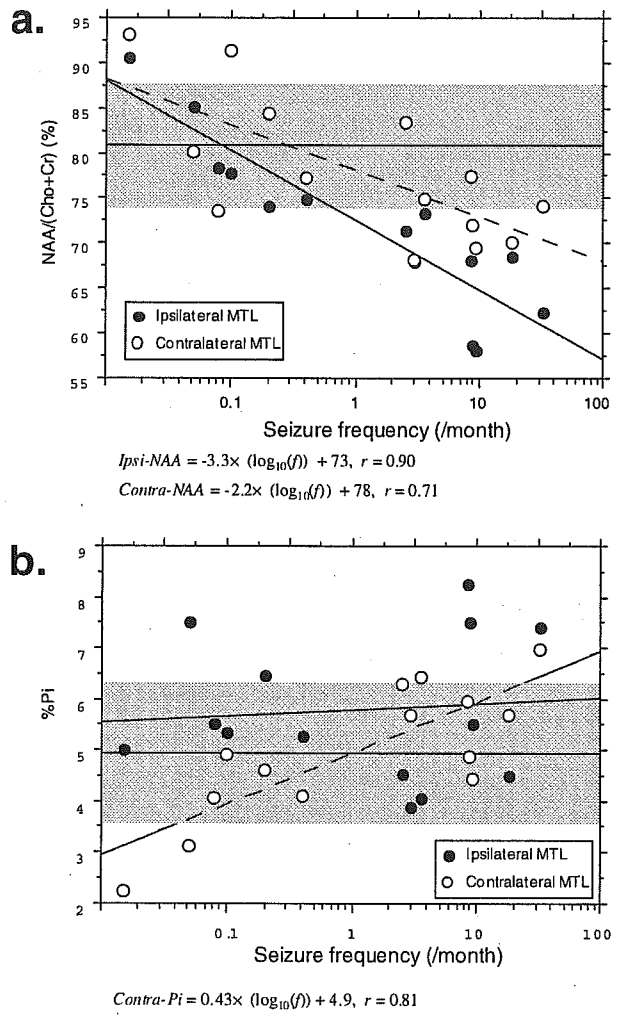

Figure 1. (a) Correlation of seizure frequency *vs* NAA/(Cho + Cr) ratio and (b) seizure frequency *vs* %Pi ratio. Logarithmic transformation was used to normalize seizure frequencies. Horizontal lines and gray areas show mean values and standard deviations of the controls. The lines represent the expected values in contralateral (dotted line) and ipsilateral (solid line) medial temporal lobes to the focus obtained by linear regression. Both ipsilateral and contralateral NAA/(Cho + Cr) were significantly correlated with the seizure frequency ($r = -0.90$, $P < 0.0001$; $r = -0.70$, $P < 0.005$, respectively; Fig. 1a). The contralateral %Pi values showed significant correlation with seizure frequency ($r = 0.81$; $P < 0.001$) but, as the ipsilateral values were very scattered, no significant result was obtained. f, seizure frequency; Ipsi-NAA, ipsilateral NAA/(Cho + Cr); contra-NAA, contralateral NAA/(Cho + Cr); Contra-Pi, contralateral %Pi.

with the seizure frequency ($r = 0.09$, Fig. 1b). Four cases with disagreement between the results from ^{31}P MRS and clinical data were in the high seizure-frequency group (> 1/month). The %Pi values in the contralateral MTL of all the low seizure-frequency group patients were lower than the mean value of the normal control, while those in six of eight patients in the high seizure-frequency group were higher than the mean value of normal control, resulting in significant correlation ($r = 0.81$; $P < 0.001$, Fig. 1b).

DISCUSSION

Significant changes in the NAA/(Cho + Cr) ratio of ^{1}H MRS and the %Pi ratio of ^{31}P MRS in the medial temporal lobes of TLE patients were observed. Both seem useful for the detection of TLE lateralization, but they have different tendencies.

The values of NAA/(Cho + Cr) in ^{1}H MRS showed significant differences between ipsilateral and contralateral MTL of TLE patients. Although %Pi also had a tendency to show the laterality of TLE, there was no significance. This indicates that ^{1}H MRS may be more useful for generally assessing the lateralization of the TLE focus. Most previous studies have shown that TLE patients have lower NAA values in their ipsilateral MTL in ^{1}H MRS. As N-acetylasparate is mainly located in neural cells, a reduction in NAA value is believed to reflect some neural damage.[3–13] In contrast, the concentrations of Cho and Cr are much higher in astrocytes and oligodendrocytes than in neurons,[19] meaning that changes in their values may reflect reactive astrocytosis. Thus, the decrease in NAA/(Cho + Cr) ratios in ipsilateral MTL may reflect neuronal loss and reactive gliosis as observed in medial temporal sclerosis in TLE patients. We also found a significant correlation between NAA/(Cho + Cr) and the seizure frequency of TLE patients, suggesting that ^{1}H MRS is useful not only for assessment of TLE lateralization but also for evaluation of TLE severity. Significant correlation between contralateral NAA/(Cho + Cr) and the seizure frequency was also detected, suggesting that neural damage due to TLE extended to the contralateral MTL in the high-seizure frequency group.

Although the mean value of %Pi in ipsilateral MTL was higher than in normal controls, the values were widely scattered, and no significant correlation with the seizure frequency was detected. The mean value of %Pi in the contralateral MTL in the low seizure-frequency group (< 1/month) was lower than that of normal controls. The %Pi increase is believed to reflect dysfunction of energy metabolism.[16] These results may indicate a hyper-energy status in the contralateral MTL as compensation for dysfunction in the ipsilateral MTL.[15] In contrast, the mean value of %Pi in the contralateral MTL in the high seizure-frequency group (> 1/month) was higher than that of normal controls. This seems to indicate a spreading of neural dysfunc-