Neural Interaction of the Amygdala with the Prefrontal and Temporal Cortices in the Processing of Facial Expressions as Revealed by fMRI

Tetsuya Iidaka[1], Masao Omori[1], Tetsuhito Murata[1], Hirotaka Kosaka[1], Yoshiharu Yonekura[1], Tomohisa Okada[2], and Norihiro Sadato[2]

Abstract

■ Some involvement of the human amygdala in the processing of facial expressions has been investigated in neuroimaging studies, although the neural mechanisms underlying motivated or emotional behavior in response to facial stimuli are not yet fully understood. We investigated, using functional magnetic resonance imaging (fMRI) and healthy volunteers, how the amygdala interacts with other cortical regions while subjects are judging the sex of faces with negative, positive, or neutral emotion. The data were analyzed by a subtractive method, then, to clarify possible interaction among regions within the brain, several kinds of analysis (i.e., a correlation analysis, a psychophysiological interaction analysis and a structural equation modeling) were performed. Overall, significant activation was observed in the bilateral fusiform gyrus, medial temporal lobe, prefrontal cortex, and the right parietal lobe during the task. The results of subtraction between the conditions showed that the left amygdala, right orbitofrontal cortex, and temporal cortices were predominantly involved in the processing of the negative expressions. The right angular gyrus was involved in the processing of the positive expressions when the negative condition was subtracted from the positive condition. The correlation analysis showed that activity in the left amygdala positively correlated with activity in the left prefrontal cortex under the negative minus neutral subtraction condition. The psychophysiological interaction revealed that the neural responses in the left amygdala and the right prefrontal cortex underwent the condition-specific changes between the negative and positive face conditions. The right amygdaloid activity also had an interactive effect with activity in the right hippocampus and middle temporal gyrus. These results may suggest that the left and right amygdalae play a differential role in effective processing of facial expressions in collaboration with other cortical or subcortical regions, with the left being related with the bilateral prefrontal cortex, and the right with the right temporal lobe. ■

INTRODUCTION

It has been suggested that the amygdala, on which highly processed sensory information from all modalities converge, plays a critical role in motivated or emotional behavior (Ono, Nishijo, & Uwano, 1995; Aggleton, 1992; Nishijo, Ono, & Nishino, 1988; Iwai & Yukie, 1987). Bilateral damage to the human amygdala causes severe impairments in recognition of emotion in facial expression, and in social judgment based on facial expression (Adolphs, Tranel, Damasio, & Damasio, 1994, Adolphs, Tranel, & Damasio, 1998). In neurophysiological studies in monkey, some neurons in the amygdala have been found to selectively respond to facial stimuli (Nakamura, Mikami, & Kubota, 1992; Leonard, Rolls, Wilson, & Baylis, 1985). Recent neuroimaging studies also demonstrated significant activation in the human amygdala during tasks involving emotional faces (Hariri, Bookheimer, & Mazziotta, 2000; Blair, Morris, Frith, Perrett, & Dolan, 1999; Whalen et al., 1998; Phillips et al., 1997; Breiter et al., 1996; Morris et al., 1996, 1998). A particularly notable finding is that the left amygdala was more greatly activated during the processing of fearful expressions than during the processing of happy expressions (Morris et al., 1996, 1998). Further, an increasing intensity of sad facial expressions was associated with enhanced activity in the left amygdala (Blair et al., 1999). The involvement of the left hemisphere in the perception of fearful expressions may be inconsistent with the notion that the right hemisphere is involved in the recognition of facial emotion (Bowers, Blonder, Feinberg, & Heilman, 1991), particularly in the case of recognition of negative expressions (Reuter-Lorenz & Davidson, 1981). However, Sergent and Bindra (1981) noted that the right-hemisphere advantage may depend on the conditions that make holistic processing of the facial stimuli possible; that is, if the conditions require analytic judgment, the left-hemisphere advantage may occur. Several studies of patients with brain damage showing left-hemispheric involvement in the

[1]Fukui Medical University, Japan, [2]National Institute for Physiological Sciences, Japan

verbal or categorical judgment of facial expressions (Stone, Nisenson, Eliassen, & Gazzaniga, 1996; Young, Newcombe, de Haan, Small, & Hay, 1993) support this hypothesis.

The involvement of the left amygdala in the processing of negative facial expressions may be associated with analytical or categorical judgment, but it is unlikely that the amygdala is solely responsible for these processes; the amygdala is not a site of memory storage on which the judgment of stimuli may depend. Rather, it is reasonable to assume that the amygdala serves to influence memory-storage processes in other brain regions, such as the hippocampus and the neocortex (Cahill & McGaugh, 1998). A possible candidate for the brain region that interacts with the amygdala is the prefrontal and temporal cortices, because these regions are heavily and reciprocally connected (Carmichael & Price, 1995; Amaral, Price, Pitkanen, & Carmichael, 1992; Barbas & De Olmos, 1990). A study in monkey showed that the surgical disconnection of the amygdala from the inferior temporal or prefrontal cortices impaired stimulus–reward associative learning (Gaffan, Gaffan, & Harrison, 1988, Gaffan, Murray, & Fabre-Thorpe, 1993). A neuroimaging study in humans also showed neuromodulatory effects of the right prefrontal cortex on the amygdala during a face-labeling task (Hariri et al., 2000), although the precise role of the effect is still unclear. The present study aimed at investigating the neural interaction between the amygdala and other cortical or subcortical regions using functional magnetic resonance imaging (fMRI) and face stimuli with negative (anger and disgust), positive (happy), and neutral emotional valence, respectively. The subjects were scanned while they were judging the sex of the faces; thus, perception of the emotional valence was implicitly implemented in the experiment. We predicted that the left amygdaloid activity would be greater during the processing of negative faces than during the processing of neutral or positive faces. Given that the limbic–cortical network subserves the effective processing of these emotional stimuli, it was possible to predict that the activity of the amygdala would parallel the activity of the other cortical or subcortical regions, and that functional relevance between the two regions would be modulated by the experimental conditions. These hypotheses were tested using a subtraction analysis, correlation analysis, and psychophysiological interaction according to the general linear model (Elliott & Dolan, 1998; Friston et al., 1995, 1997). Finally, functional integration involving the amygdala and other temporal lobe regions was examined using structural equation modeling (Büechel & Friston, 1997).

RESULTS

Behavioral Data

The mean (± *SD*) percentage of correct responses given by the subjects was 98 ± 4% for the negative face condition, 99 ± 1% for the positive face condition, and 99 ± 2% for the neutral face condition. The subjects performed at ceiling level in responding to the control condition (over 99% correct).

Neuroimaging Data

Main Effect of Face Task

Areas of significant activation during the face task determined by averaging three face conditions are shown in Table 1 and Figure 1. Activation was observed in the bilateral prefrontal cortices (BA 44/46/9), fusiform gyrus (BA 37), medial temporal lobe, and the

Table 1. Areas of Significant Activation During the Task Averaging Three Conditions

L/R	*Region*	*BA*	*Z Value*	*Coordinate*
R	Inferior frontal gyrus	44/46	5.57*	46, 14, 26
L	Middle frontal gyrus	9	4.20*	−36, 8, 34
R	Fusiform gyrus	37	5.55*	40, −78, −16
L	Fusiform gyrus	37	4.85*	−38, −76, −16
R	Amygdala		4.33*	16, −6, −18
L	Amygdala		4.47*	−16, −6, −18
R	Hippocampus		4.05*	34, −16, −16
R	Angular gyrus	39	4.27	32, −66, 36
R	Lingual gyrus	19	4.17*	22, −70, 2

L: Left; R: Right; BA: Brodmann's area.

*Significance at $p = .05$ after correction for multiple comparison at the cluster level.

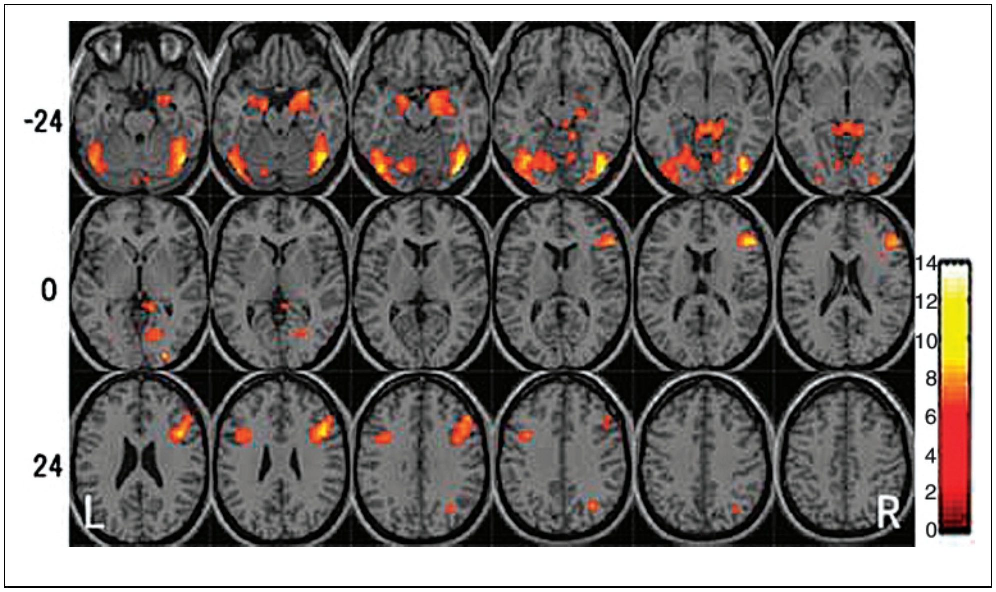

Figure 1. Areas of significant activation during the task averaging three face conditions are superimposed on the T1 template image (from −24 to +44 mm relative to AC–PC line in 4-mm increments). Numbers on the left of the figure are levels of *z*-axis according to Talairach coordinate. Statistical threshold is set at $p = .001$ (uncorrected), and the clusters larger than 30 contiguous voxels are shown. Significant activation in the bilateral fusiform gyrus, prefrontal cortex, medial temporal lobe including the amygdalae, and the right parietal lobe is indicated. The coordinates of the activated clusters are listed in Table 1.

right parieto-occipital lobe. The medial temporal lobe activation included the bilateral amygdalae and the right hippocampus.

Activation Related to the Processing of Facial Expressions

The subtraction of the neutral condition from the negative condition revealed the neural substrates predominantly involved in the processing of negative expressions in the left amygdala (Table 2, Figure 2-top) and the right orbitofrontal cortex. The magnitude of activation from the control condition in the left and right amygdaloid region was plotted as a function of the peristimulus time during each emotional block, as shown in Figure 3. The signal in the left amygdaloid region was significantly greater under the negative condition than under the positive or neutral one [$F(2,359) = 4.45$, $p < .05$, post hoc test, negative vs. neutral $p < .01$, negative vs. positive $p < .05$], whereas the signal in

Table 2. Areas Specifically Associated with the Processing of Facial Expressions

L/R	*Region*	*BA*	*Z Value*	*Coordinate*
a) Negative expression minus neutral expression				
R	Superior temporal gyrus	38	3.84	34, 6, −20
L	Superior temporal gyrus	38	3.35	−38, 4, −22
R	Orbitofrontal cortex	11	3.75	12, 2, −20
L	Amygdala		3.33*	−26, 4, −14
R	Middle temporal gyrus	21	3.41	56, −2, −20
b) Positive expression minus neutral expression				
No significant voxel				
c) Positive expression minus negative expression				
R	Angular gyrus	39	3.83	44, −72, 34
d) Negative expression minus positive expression				
L	Middle temporal gyrus	21	3.79	−48, 0, −26
L	Inferior frontal gyrus	44	3.69	−30, 6, 22
L	Precentral gyrus	4	3.38	−34, −10, 46

*Significance at $p = .05$ after multiple comparison at the cluster level (search region was restricted to amygdala).

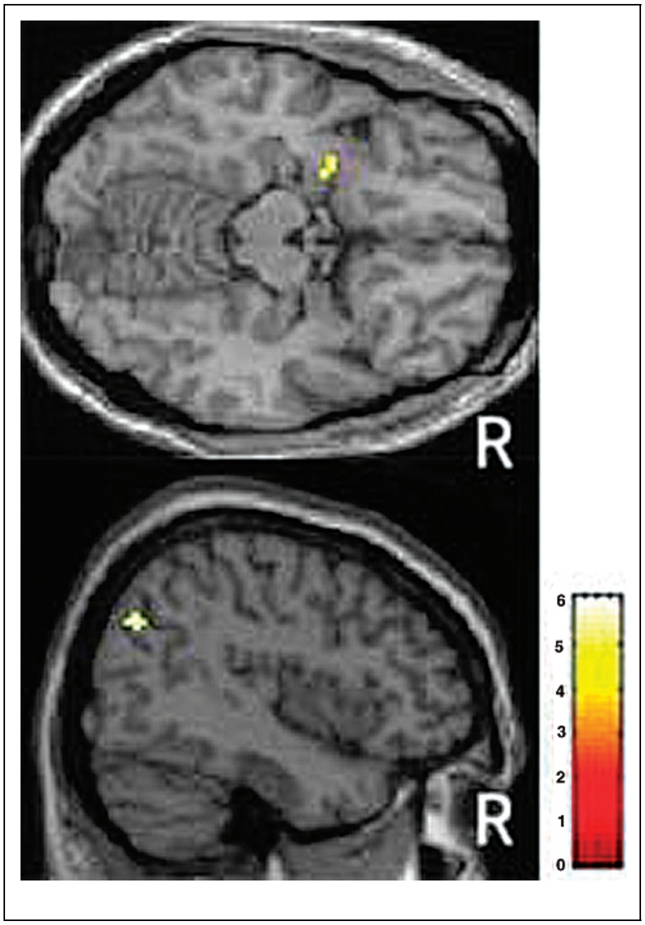

Figure 2. Brain regions specifically associated with the processing of emotional expressions are superimposed on the T1 template image. Top: Activity in the left amygdala was significantly greater under the negative face condition than under the neutral face condition. Bottom: Activity in the right angular gyrus was significantly greater under the positive face condition than under the negative face condition. The coordinates of the clusters are listed in Table 2. Statistical threshold is set at $p = .001$ (uncorrected).

the right amygdaloid region was comparable among the three conditions [$F(2,359) = .48, p = .61$]. Other areas predominantly related to the processing of negative expressions were found in the bilateral temporal pole and the middle temporal gyrus. No significant area of activation was observed in the subtraction between the positive and neutral condition. The positive condition had significantly greater activity than the negative condition in the right angular gyrus (BA 39, Figure 2-bottom). The regions in the temporal pole, prefrontal cortex, and precentral gyrus of the left hemisphere had greater activity during the negative condition than during the positive condition.

Correlation Between Signal Changes in the Amygdala and Other Cortical Areas

The critical regions of activation identified in neuroimaging studies for perception of emotional faces are in the amygdala. The present study also demonstrated significant activation in the left amygdala, particularly under the negative condition as compared with the neutral condition. We sought to determine the contribution of this region to activity in other brain regions, using a correlation analysis based on activity in the maximally activated voxel in the left amygdala. The analysis revealed a significant relationship between the amygdala and the prefrontal cortex in the negative minus neutral subtraction condition. The signal change in the left amygdala positively correlated with the signal change in the left inferior frontal gyrus (BA 45; $x, y, z = -48, 34, 4$; Figure 4).

Psychophysiological Interaction

In order to illustrate functional differences between the left and right amygdala with regard to limbic–cortical interaction, a psychophysiological interaction analysis (see Methods) was performed, using activity in the left or right amygdala as a covariate. The analysis identified a prefrontal region in the right hemisphere showing condition-specific changes with left amygdaloid activity (Figure 5-top, green). Most importantly, activity in the right inferior frontal gyrus (BA 44/9; $x, y, z = 46, 4, 30$) showed a positive correlation (Figure 5-bottom, filled line; $r = .57$, $p < .05$) with activity in the left amygdala under the negative condition, but the slope was slightly negative (dotted line; $r = -.3$, *ns*) under the positive condition. The region with significant psychophysiological interaction overlapped with the prefrontal region, which showed significant activation during the face task (Figure 5-top, red). Activity in the right amygdala showed a positive correlation with activity in the right hippocam-

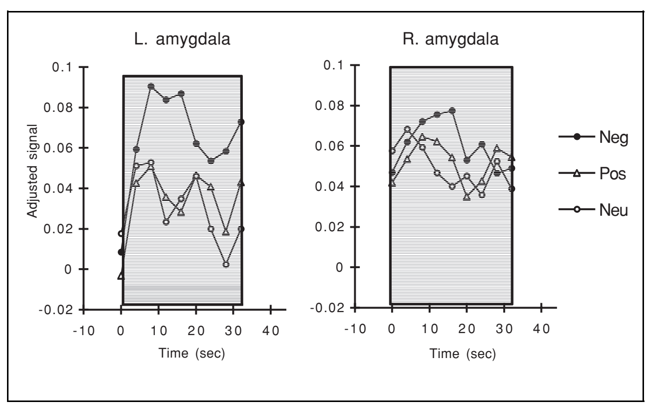

Figure 3. Signal time courses under each of the three face conditions extracted from the left and right amygdaloid regions are plotted as a function of time (see Methods). The shaded area represents a task block with a duration of 32 sec and nine image acquisitions. Throughout a block, 12 face pairs with a single emotional category were presented. Predominant activation in the left amygdala is observed under the negative condition (filled circles), whereas activity in the right amygdala is comparable among the three conditions. Neg: negative face condition; Pos: positive face condition; Neu: neutral face condition.

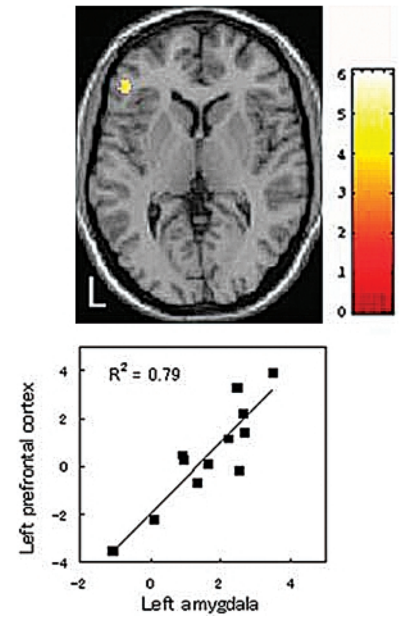

Figure 4. Top: The result of the correlation analysis is superimposed on the T1 template image at the level of $z = 4$ mm. Activity in the left inferior frontal gyrus had a significant positive correlation with activity in the left amygdala. Bottom: Plots and a regression coefficient of the significant correlation between signal changes in the left amygdala (x-axis) and the left prefrontal cortex (y-axis), under the negative minus neutral subtraction condition.

pus under the neutral condition (Figure 6-top; x, y, z = 28, −12, −18; $r = .62$, $p < .05$), whereas the slope was negative ($r = -.62$, $p < .05$) under the negative condition. This pattern of interaction was also found between the right amygdala and the right middle temporal gyrus (Figure 6-middle and bottom, BA 39; x, y, z = 40, −62, 24; dotted line $r = .5$ and filled line −0.64, $p < .05$).

Structural Equation Modeling

Functional integration within the right temporal lobe as delineated by the psychophysiological interaction analysis was examined using a structural equation modeling. The analysis used adjusted signal data in the three functionally related regions in the right temporal lobe. The result is schematized in Figure 7. Under both negative and neutral conditions, the hypothesized model is statistically insignificant (negative condition χ^2 = 2.89, $p = .09$; neutral condition $\chi^2 = 3.12$, $p = .08$), that is, the model is able to reproduce the observed variance–covariance structure (Büechel & Friston, 1997). Activity in the right amygdala had positive path coefficients to the right hippocampus and middle temporal gyrus under the neutral condition, whereas these coefficients were negative under the negative condition. Coefficients of the efferent paths from the amygdala were greater than those of the afferent paths to the amygdala under both conditions.

DISCUSSION

The present results showing distributed cortical and subcortical activation as the main effect of the task averaging three face conditions are in line with results in previous neuroimaging studies using a face-matching task (Grady et al., 1994) or face-encoding task (Kelley et al., 1998). A particularly notable finding is that the present study demonstrated predominant activation in the bilateral amygdaloid regions, suggesting a role of amygdala in face processing (Nakamura et al., 1992; Leonard et al., 1985).

Areas Related to the Processing of Emotional Expressions

The first aim of this study was to test whether the processing of negative expressions (i.e., faces depicting anger or disgust) activates the amygdaloid region to a

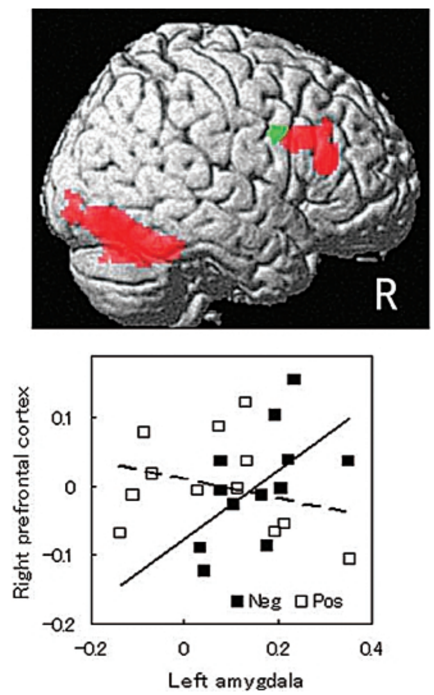

Figure 5. Top: The results of the psychophysiological interaction are superimposed on the surface of the standard brain. A prefrontal region in the right inferior frontal gyrus showed condition-specific signal changes with the left amygdaloid activity. In the area in green, an interaction was observed between the negative and positive conditions. The red area represents significant activation during face task averaging the three face conditions (thresholded at $p = .0001$). Bottom: Plots and regression lines show significant interaction between neural activity and the experimental condition. The x-axis represents activity in the left amygdala and the y-axis represents activity in the right prefrontal cortex (green in the top figure). Under the negative condition, a positive correlation was observed between activities in these two regions (filled squares and filled line), whereas under the positive condition, a correlation between activities for the same voxels was slightly negative (open squares and dotted line).

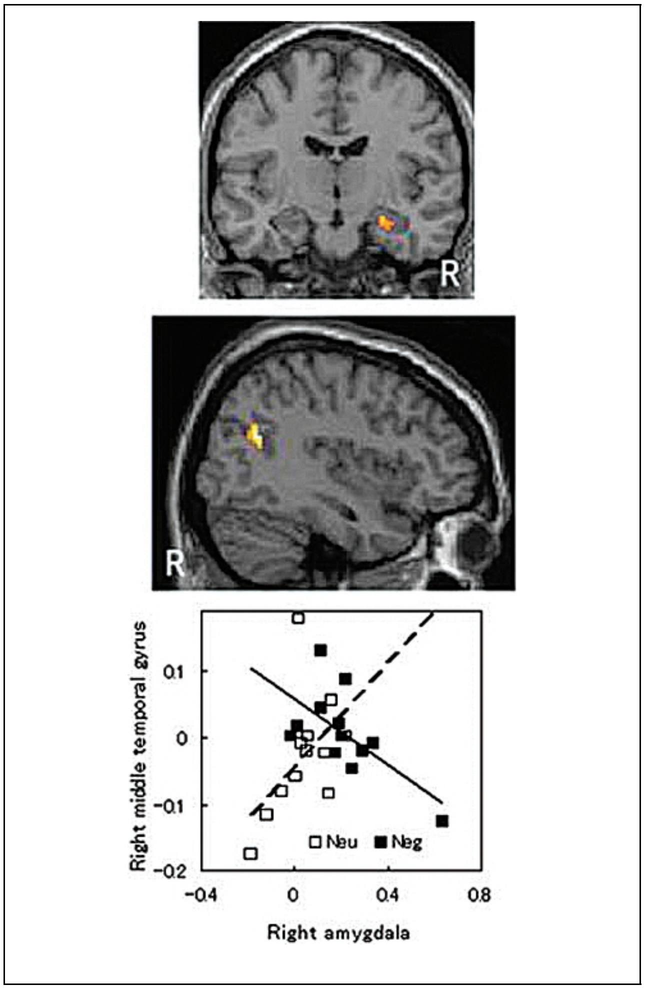

Figure 6. The results of the psychophysiological interaction are superimposed on the T1 template image. The right hippocampus (top) and the middle temporal gyrus (middle) showed condition-specific signal changes with the right amygdaloid activity. In these regions, an interaction was observed between the negative and neutral conditions. Bottom: Plots and regression lines show significant interaction between neural activity and the experimental condition. The *x*-axis represents activity in the right amygdala and the *y*-axis represents activity in the right middle temporal gyrus. Under the negative condition, a negative correlation was observed between activities in these two regions (filled squares and filled line), whereas under the neutral condition a correlation between activities for the same voxels was positive (open squares and dotted line).

greater degree than the processing of neutral or positive expressions does. The results showing significant activation in the left amygdala under the negative minus neutral subtraction condition confirmed our hypothesis. A plotting of signal time course in the amygdaloid regions also showed prominent activity in the left amygdala under the negative condition. In the right amygdala, the magnitude of activation from the control condition was comparable among all of the face conditions. Neuroimaging studies have found greater activation in the left or bilateral amygdala during tasks with fearful expressions than during tasks with neutral (Phillips et al., 1997; Breiter et al., 1996) or happy expressions (Morris et al., 1996); however, the involvement of the amygdala in the processing of disgusted or angry faces has not been reported (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998; Phillips et al., 1997). There may be several reasons for the inconsistency between the previous studies and the present one. First, the number of individuals whose faces were used as the experimental stimuli was larger in the present study ($n = 24$) than in the previous one ($n = 8$). Several studies using faces showed significant effects of habituation on amygdaloid activity, with reduced signals resulting as the number of repetitions increases (Whalen et al., 1998; Breiter et al., 1996). We speculate that the previous studies failed to detect significant activation due to the habituated responses in the amygdala. Second, we presented the faces as pairs with their counterpart randomly interchanged, while the previous investigators used a single face as stimuli. The difference in the number of emotional stimuli might affect sensitivity for detecting significant amygdaloid responses. Third, a behavioral study of nine individuals with bilateral amygdala damage showed that they did not correctly recognize angry or disgusted faces (Adolphs et al., 1999). The results strongly suggest an involvement of the human amygdala in perceiving angry and disgusted faces as well as fearful ones, and support the present finding with predominant activation in the amygdala under the negative condition. There was also activation related to the negative condition in the right orbitofrontal cortex, in which dense and reciprocal anatomical connection with amygdala has been reported (Barbas & De Olmos, 1990). Activation in the cortical

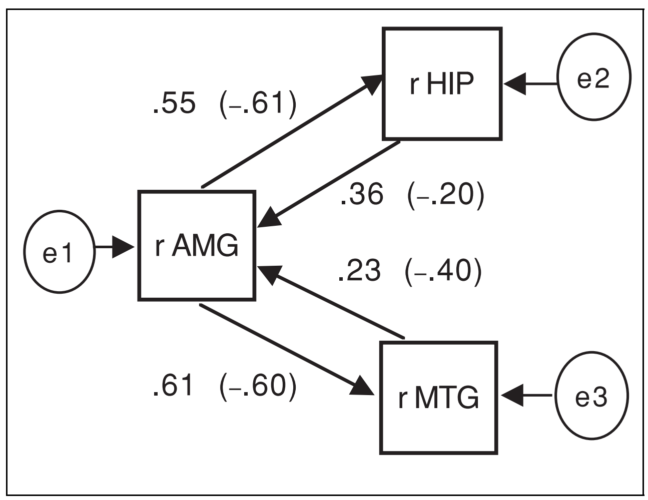

Figure 7. A path diagram from the analysis using structural equation modeling involving the amygdala (r AMG), hippocampus (r HIP), and middle temporal gyrus (r MTG) of the right hemisphere is shown. The values of the standardized path coefficients under the neutral condition (without parenthesis) and under the negative condition (with parenthesis) are indicated. Path coefficients between the amygdala and the other two regions are positive under the neutral condition and negative under the negative condition. The influence of the amygdaloid activity on activity in the other regions is greater than vice versa.

regions in the temporal pole under the negative condition appears to reflect higher-order processing of faces; this area receives visual input from unimodal or heteromodal sensory cortices (Ungerleider, 1995) and projects information to the amygdala (Iwai & Yukie, 1987). Phillips et al. (1997) showed signal increases related to the perception of disgusted faces in the insula and the posterior cingulate gyrus. We also found significant activation of the left insula ($x, y, z = -36, 0, -8$; $Z = 3.26$) and of the posterior cingulate gyrus ($x, y, z = -4, -54, 8$; $Z = 4.27$) in the negative minus neutral subtraction. However, these clusters were not reported because a cluster in the left insula did not survive extent threshold ($k > 10$), and the posterior cingulate gyrus had a large signal decrease under the neutral condition rather than a signal increase under the negative one.

The positive minus negative subtraction condition revealed activity specifically associated with the processing of positive expressions in the right angular gyrus. The activated area was located adjacent to the posterior part of the superior temporal gyrus, which has been found to be involved in the perception of eye gaze (Hoffman & Haxby, 2000; Campbell, Heywood, Cowey, Regard, & Landis, 1990; Perrett et al., 1985). This finding may suggest that during the positive condition the subjects were more attentive to the facial expression around the posers' eyes than they were during the negative condition. Breiter et al. (1996) found significant involvement of the temporo-occipital region and amygdala in the processing of happy faces. In the present results, the activity in the right middle temporal gyrus (BA 39; $x, y, z = 52, -70, 16$; $Z = 3.22$) and in the parahippocampal gyrus ($x, y, z = 12, -44, 4$; $Z = 3.47$) was greater under the positive condition than under the neutral condition; however, the spatial extent of these clusters did not survive the statistical threshold ($k > 10$). The result in this study showing that the amygdala was not significantly activated in the positive minus neutral subtraction, even at the lenient threshold ($p = .01$, uncorrected), is inconsistent with the result obtained by Breiter et al. However, both group analyses using the random effect model, and observation of the time-course data averaging 12 subjects yielded the identical result that amygdaloid activation was comparable between the positive and neutral conditions. In addition, studies of patients with bilateral amygdala damage showed that the subjects were impaired at recognizing negative faces, but not at recognizing happy faces (Adolphs et al., 1998, 1999). The results imply that amygdala is specifically involved in perceiving negative faces. It is possible that the use of a block design in the present study limited the sensitivity for detecting significant differences in activation between the conditions. Another reason that accounts for the inconsistencies between the present and previous results may be due to individual differences. For example, an fMRI study by Canli et al. (2001) showed that activity in the cortical and subcortical region, including the prefrontal cortices and amygdala, had significant correlation with the subject's personality traits. Further study employing an event-related design and more uniformly controlled subjects with regard to their personality may enable us to elucidate more precisely the neural substrates involved in the processing of facial expressions.

Neuromodulatory Effects of Amygdala

Prefrontal Cortex

The result of correlation analysis identified a prefrontal area in the left hemisphere that interacted with the amygdala under the negative minus neutral subtraction condition. As shown in Figure 4, the subject with greater activity in the left amygdala had greater activity in the left prefrontal cortex. The limbic–cortical interaction observed in the present study may imply, albeit indirectly, that the processing of negative expressions is modulated by the neural interaction between the prefrontal cortex and the amygdala in the left hemisphere. This hypothesis may be inconsistent with the general notion that the processing of facial expressions, particularly that of the negative facial expressions, is mediated in the right hemisphere (Bowers et al., 1991; Reuter-Lorenz & Davidson, 1981). However, another study showed that patients with damage in the left hemisphere had selective impairments in matching and recognition of facial expression (Young et al., 1993), which might be related with an involvement of verbal labeling during such tasks (Stone et al., 1996). Sprengelmeyer et al. (1998) showed that the left inferior frontal gyrus responded to faces depicting disgust or anger when compared with neutral faces. The regional blood flow in the left inferior frontal gyrus enhanced with increasing intensity for the fearful face (Morris et al., 1998). A neuroanatomical study showed that the ventrolateral prefrontal cortex had neural projections to the amygdala (McDonald, Mascagni, & Guo, 1996). The neurons in this prefrontal area receive information mainly from the superior temporal gyrus, where activity of face selective neurons was recorded (Hasselmo, Rolls, & Baylis, 1989). Thus, the finding from these studies and from ours indicates an integrative role of the left inferior frontal lobe and amygdala in the processing of information derived from negative facial expressions. Elliott, Dolan, & Frith (2000) reviewed neuroimaging studies that showed selective involvement of the ventral part of the frontal lobe. These studies suggested that this region is likely to be activated when a response previously associated with reward is suppressed. A response to the negative faces observed in our study may relate to social situations in which a negative expression is an important signal to inhibit the current choice of behavior.

The results of psychophysiological interaction indicated that activity in the right prefrontal cortex had condition-dependent covariation with activity in the left amygdala. A positive correlation between right prefrontal activity and left amygdaloid activity was maximally observed under the condition of negative expressions (Figure 5, filled square and filled line), whereas the slope was slightly negative under the condition of positive expressions (open squares and dotted line). The prefrontal cluster overlapped considerably with the prefrontal region, which was activated during the face tasks. In contrast, Hariri et al. (2000) found a negative correlation between left amygdaloid activity and right prefrontal activity during a labeling task involving negative expressions. However, in their analysis, which included only a verbal labeling task of expressions, the neural interaction between the different task conditions was not fully elucidated. In the present study, single task instruction (i.e., gender discrimination) was used, and the subjects therefore should have used the same strategy under each of the three face conditions. Nevertheless, we found condition-specific changes of activity between the conditions, indicating that a perceptional feature of emotional expressions, but not the subject's strategy, modulated neural activity in the amygdala and prefrontal cortex.

The limbic–cortical interaction found in the psychophysiological interaction analysis suggests a neuromodulatory role of the left amygdala and the right prefrontal cortex during the processing of emotional expressions. Because projections from the left amygdala to the prefrontal cortex are found mainly in the ventromedial regions of the left hemisphere (Carmichael & Price, 1995), the interaction found in the present study should be mediated by other brain regions. One of such region may be the mediodorsal thalamic nucleus (MD), which receives projections from almost all of the amygdaloid nuclei (Amaral et al., 1992). MD has rich anatomical connections with both the medial and lateral part of the prefrontal cortex (Goldman-Rakic & Porrino, 1985). Indirect disconnection of the amygdala from the prefrontal cortex by ablating MD produced an impairment of stimulus–reward associative memory in monkeys (Gaffan et al., 1993). Thus, it is possible that the amygdala interacts with the frontal lobe by two partially independent pathways, one pathway being dependent on MD, and the other on the ventromedial prefrontal cortex. Another candidate is the amygdalostriatal projection, which involves not only the ventral striatum, but the caudate nucleus and putamen (Amaral et al., 1992). This projection could activate the corticostriatal loop through the thalamus and the prefrontal cortex (Alexander, Crutcher, & DeLong, 1990). Two fMRI studies reported that a region in the right dorsolateral prefrontal cortex had predominant activity during tasks related to response inhibition (Garavan, Ross, & Stein, 1999; Konishi et al., 1999). Positive covariation between the left amygdaloid activity and the right prefrontal activity under the negative condition found in the present study may reflect neural mechanisms for suppressing inappropriate responses to aversive stimuli in social contexts. The results, including those in the present study, suggest that the neural network involving these regions plays a crucial role in learning the associations between stimuli and reinforcement, and subsequently in the social behavior of humans by effectively processing the emotional valence of facial expressions.

Temporal Lobe and Hippocampus

A region in the right hippocampus and middle temporal gyrus also played a neuromodulatory role under the negative and neutral conditions. The right amygdala had a negative covariation with these two regions in the right temporal lobe, specifically during presentation of the negative faces. Although the present study does not directly investigate neural interaction between the regions, the results are consistent with the amygdala's known anatomical connection with the hippocampus or with early visual cortices (Amaral et al., 1992; Iwai & Yukie, 1987). A study in monkeys showed that disconnection of the inferotemporal area from the amygdala impaired the learning of associations between visual stimuli and food reward (Gaffan et al., 1988). A PET study in humans also found a neuromodulatory role of the amygdala and temporo-occipital regions during presentation of negative and of happy faces (Morris et al., 1998). Moreover, activity in the amygdala is found to influence memory-related processes in the hippocampus, such as long-term potentiation at a neuronal level (Akirav & Richter-Levin, 1999). In our structural equation modeling, we determined a simple anatomical model involving these three regions in the right temporal lobe. The results suggest that activity in the amygdala has a greater influence on activity in the hippocampus or early visual cortex, than vice versa. Emotional information about faces may be carried via backprojections from the amygdala to the hippocampus, where they become linked into episodic memory. Neural interaction between the back projections and forward projections involving the amygdala and early visual cortices could modify synaptic activity in the temporo-occipital visual pathway to influence later cognitive processing by facilitating or inhibiting some perceptual representations (Aggleton, 1992).

Differential Role of the Left and Right Amygdalae

The results of our subtraction analysis showed that the left amygdala was predominantly involved in the processing of the negative faces, but that right amygdaloid activity did not differ among the conditions. Activity in the left amygdala covaried with activity in the left ventrolateral and right dorsolateral prefrontal cortices, whereas the right amygdala had interaction with the hippocampus and temporal cortex of the right hemisphere. These experimental findings suggest a differential role of the left and right amygdalae in the processing of facial expressions. Several neuroimaging studies have found that left amygdaloid activity was associated with the perception of negative faces (Wright et al., 2001; Blair et al., 1999; Morris et al., 1996). The left amygdaloid involvement in the processing of the stimuli with negative emotional valence was also observed when scenes or pictures were used as stimuli (Canli, Zhao, Brewer, Gabrielli, & Cahill, 2000; Taylor et al., 1998). These results may indicate a specific neurophysiological role of the left amygdala in the processing of information with negative emotional valence, regardless of the type of stimuli. The correlation of activity between the left amygdala and the prefrontal cortices found in the present study would imply that the effective processing of these negative stimuli is based on the activation of the amygdalo–prefrontal loop, which is mediated by direct or indirect neural connection.

However, few neuroimaging studies have reported a specific role of the right amygdala in the processing of faces. Wright et al. (2001), for example, found a significantly greater habituation effect in the right amygdala while viewing facial expressions as compared with the left amygdala. In the present study, the magnitude of activation in the right amygdala was not statistically different among the different face conditions. This finding would imply that the right amygdala generally responds to the presentation of a face regardless of the emotional valence expressed by that face. However, activity in this region differed among the conditions, in that interregional connectivity between the amygdala and other cortical and subcortical regions in the temporal lobe was specifically modulated by the facial expression. Taken together, the present study suggests that the left amygdala is specifically associated with information with the negative valence under the functional integration with the prefrontal cortices, and the right amygdala is generally involved in the face processing, but modifies functional connectivity within the right temporal lobe.

The Effect of Habituation

During the face task, three experimental blocks each assigned to a different face condition were successively presented to the subject. We investigated the effect of order of presentation on brain activity by analyzing signal changes between the first, second, and third presentation. The result revealed significant habituation effect within the face block on neural activity in the posterior part of the parahippocampal gyrus (x, y, z = 14, −42, −8; p = .005). In addition, the effect of repetition of the face task (four repetitions within a run) on brain activity was found in the left cerebellum (x, y, z = −14, −56, −40; p = .001). The habituation effects on amygdaloid activity that were reported previously (Whalen et al., 1998; Breiter et al., 1996) were not observed in the present study, even at a lenient threshold (p = .01).

METHODS

Subjects

Twelve young (six male and six female, mean age 25.1 ± 5.0 years) subjects participated in the study after giving written informed consent. The subjects' physical health was verified in an interview before the study, and those who had a history of neurological diseases, psychiatric diseases, or drug or alcohol abuse were excluded. No subject was taking drugs that could affect the cerebral blood flow at the time of the study. Except for one subject who was ambidextrous, all subjects were strongly right-handed (assessed by the Edinburgh Handedness Inventory). The protocol for this study was approved by the ethics committee at Fukui Medical University. Prior to the experiment, a shorter version of the experimental task involving neutral faces was administered in order to confirm that subjects could perform at an average level.

Task Paradigm

Digitized grayscale pictures of 24 unfamiliar faces (12 male and 12 female) with negative, positive, or neutral emotional valence were used. Prior to the experiment, the validity and reliability of the portrayal of emotion in these pictures were tested in another group of subjects (n = 10). The subject was told to label the emotion expressed by the face as negative or positive and to rate the intensity of the emotion on a 5-point scale. The probability that the facial expression was correctly labeled was 98% for the negative expressions and 99% for the positive expressions. The majority of the subjects (78%) categorized the negative faces as having an angry or disgusted expression, and nearly all of the subjects (99%) categorized the positive faces as having a happy expression. Thus, in the present study, the neural substrate involved in the perceiving of a "negative" face condition is considered to be a reflection of the combination of cognitive processes for perceiving angry and disgusted faces. Several behavioral studies have shown that among the six basic expressions, anger and disgust were perceived to be similar (Adolphs et al., 1999; Russell & Bullock, 1985). The results of a recognition task for these two expressions were considerably intermixed when the subjects grouped together faces that appeared to look alike (Russell & Bullock, 1985), as well as when they labeled the expressions and rated their intensities (Adolphs et al., 1999). Therefore, it is reasonable to assume that the perception of these two expressions may share common neural substrates. The average rating scores for emotional intensity were 2.6 ± 0.3 for the negative, 2.5 ± 0.4 for the positive, and 0.1 ± 0.1 for the neutral expressions. An ANOVA performed on the rating scores revealed a significant difference between the neutral and emotional faces ($p < .01$), and no difference between the positive and negative faces.

A male face was paired with a female face with the same emotional category in order to create 12 pairs of faces with negative, positive, or neutral emotional valence. A list of the 12 pairs was assigned to each experimental block during scanning. Four repetitions of a control block (C) and three face blocks (F), with an additional control block at the end of the run, were presented to the subject (C–F–F–F–C–F–F–F–C–F–F–F–C–F–F–F–C). Each face was paired with a different face in each repetition. In each of the three emotional conditions we presented in our study, faces from the same set of 24 actors were used. The arrangement (i.e., left side vs. right side) of the male face and the female face was randomized within the list. Luminance of the face pairs was adjusted to make the images as comparable as possible. The order of the face blocks was counterbalanced across all subjects (neutral–positive–negative, negative–neutral–positive, or positive–negative–neutral). The face pairs were presented at a rate of 2.5 sec/pair with a 0.2-sec intertrial interval. During the experiment, the subject was told to judge the sex of the faces and to respond by pressing the left or right button of the response box. No particular instruction was given to pay attention to the emotional valence of the faces. Half of the male and half of the female subjects responded to the male faces, and the other half of the male and half of the female subjects responded to the female faces. As a control, the subjects were asked to discriminate the sizes of two rectangles and respond to the larger one by pressing the left or right button. The stimuli were projected onto a half-transparent screen by an LCD projector connected to a personal computer that generated the stimuli. The subject saw the stimuli through a tilted mirror attached to the head coil of the scanner. The subjects' responses were recorded in order to compute the percentage of correct responses.

Image Acquisition and Analysis

Functional images of the whole brain were acquired using the 3 T MRI system (GE, Milwaukee, USA) equipped with single shot EPI (TR = 4 sec, TE = 30 msec, Flip Angle = 90, 64 × 64 matrix and 44 slices, 2.7 mm slice thickness with a 0.3 mm gap). After discarding the first 6 images, the successive 136 images (8 images in each block) were subjected to analysis. Each block lasted 32 sec. A high-resolution anatomical image (T2-weighted) was also acquired (TR = 6 sec, TE = 68 msec, Flip Angle = 90, 256 × 256 matrix, 2D-FSE, 1.5 mm interleaved in 7 mm). The functional images were realigned to the final image by SPM99 (the Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm) and normalized to the standard space of Talairach and Tournoux (1988) by using parameters obtained from the normalization of a coregistered anatomical image to the MNI T2-weighted template. Finally, the images were smoothed by an 8-mm Gaussian kernel.

Subtraction Analysis

Statistical analysis in the present study was conducted according to the random effect model (Friston, Holmes, & Worsley, 1999) so that inferences could be made at the population level. First, the signal time course for each subject was modeled with a boxcar function convolved with a hemodynamic response function and hi-pass filtering (256 sec). The signal was proportionally scaled by setting the whole brain mean value to 100 arbitrary units. Each of the negative, positive, or neutral face conditions was contrasted with the control condition, thereby creating one contrast image per subject for each face condition. These images were entered into a "one-sample t test" to investigate the significant activation during each task. Significant signal changes for each contrast were assessed using t statistics on a voxel-by-voxel basis (Friston et al., 1995). The resulting areas of activation were characterized in terms of their peak height and spatial extent. First we investigated the main effect of the face task by analyzing the three conditions together. The statistical threshold was set to $p = .001$ (uncorrected) for height, and clusters larger than 30 contiguous voxels were reported. Second, the images for the neutral face condition were subtracted from the images for the negative and positive face conditions, respectively, to determine the neural substrates of emotional face processing (the contrast was inclusively masked by the main effect of face task at $p = .5$). A subtraction between the images for the negative condition and the images for the positive condition was also conducted. The statistical threshold was set to $p = .001$ (uncorrected) for height, and clusters larger than 10 contiguous voxels were reported. The amygdaloid activation was considered significant at $p = .05$ after correction for multiple comparison in a 2 × 2 × 2 cm search region (Morris et al., 1996). For all analysis, the region names (according to the human brain atlas of Duvernoy, 1999), Z values, and coordinates of activated foci are listed in the tables. Activated clusters were superimposed on the T1-weighted template image. Signal time courses in the amygdaloid regions under each of the three emotional conditions and one control condition were extracted from each individual subject's data set. Vectors of signal that accounted for the most variance in the set of voxels in a sphere of 8 mm radius at the significant amygdaloid activation (thresholded at $p = .001$ for 11 subjects and at $p = .005$ for 1 subject) were computed. These data were averaged across the subjects, and the magnitude of increase from the control condition was plotted as a function of time separately for each of the negative, positive, and neutral conditions.

Correlation Analysis

The aim of the analysis was to explore the neural interaction between one particular region of the brain (i.e., the amygdala) and the rest of the brain. According to the hypothesis on the modulating effects of a neocortical network on the limbic system (Hariri et al., 2000), we entered signal changes in the left amygdala obtained from the negative minus neutral subtraction condition into a simple regression analysis as covariates. In the correlation analyses, the statistical threshold was set to $p = .001$ (uncorrected) for height, and clusters larger than 30 contiguous voxels were reported. The results for the correlation analysis are plotted in Figure 4.

Psychophysiological Interaction

The second approach to investigate the neural interaction between the amygdala and other cortical or subcortical areas was an application of "psychophysiological interaction" on neuroimaging data (Friston et al., 1997). This term refers to the interaction between the psychological context and the physiological activity in the brain. The aim of the analysis is to attempt to explain the neural response in one brain region in terms of an interaction between input from a different region and experimental cognitive conditions (Elliott & Dolan, 1998). Specifically, in the present study, the signals in the right or left amygdala, as determined by the subtraction analysis between the face condition and the control condition, were used as covariates. The condition-specific regressions at every voxel were computed to test the differences between the regression slopes for the two different experimental conditions. The resulting SPM demonstrates the significant condition-specific changes in the contribution of the amygdala to other brain regions. The statistical threshold was set to $p = .001$ (uncorrected) for height, and 30 voxels for spatial extent. Here, we report the results in which either one or two of the regression slopes were statistically significant (Pearson's product moment correlation, $p < .05$). In this analysis, mean images of each condition, adjusted for global signal and physiological noises by scaling and hi-pass filtering, were used. Signals in the amygdala and other cortical foci are plotted in Figures 5 and 6.

Structural Equation Modeling

In this analysis, the variables are considered in terms of the covariance structure with parameters (interregional connection) being estimated by minimizing differences between observed covariance and those implied by a predicted model. The model consists of the anatomically separable regions, and the connection specified between those regions and their directions. The anatomical regions comprised the amygdala, hippocampus, and middle temporal gyrus of the right hemisphere, where significant psychophysiological interaction was observed (Figure 6). The model is schematized as a pathdiagram in Figure 7. Since the amygdala has a reciprocal connection with the hippocampus and with early visual cortices (Amaral et al., 1992; Iwai & Yukie, 1987), and the amygdaloid activity is suggested to influence the activity of these cortical or subcortical regions through feedback mechanisms (Akirav & Richter-Levin, 1999; Morris et al., 1998; Aggleton, 1992; Gaffan et al., 1988), we predicted that the directionality of connection would be predominantly from the amygdala to the other regions. The analysis was performed using AMOS software (version 4.01, SmallWaters, Chicago, IL, USA). Adjusted signals in the three regions extracted from the data set for psychophysiological interaction analysis under the negative and neutral conditions were entered as variables. For both conditions, a goodness-of-fit value, expressed as chi-square, was computed and the statistical threshold was set to $p = .05$. Several constraints were applied to the model: (1) the residual variances for each of the three regions were fixed at the observed variance divided by four, and (2) path coefficients from the residual variance to the observed variable were fixed at 1 (Büechel & Friston, 1997). The values of the estimated path coefficients are standardized.

Acknowledgments

This study was supported by a research grant for the "Research for the Future" Program from the Japan Society for the Promotion of Science (JSPS-RFTF97L00203).

Reprint request should be sent to Tetsuya Iidaka, School of Informatics and Sciences, Nagoya University, Nagoya, Aichi 464-8601, Japan, or via e-mail: iidaka@ info.human.nagoya-u.ac.jp.

The data reported in this experiment have been deposited in the National fMRI Data Center (http://www.fmridc.org). The accession number is 2-2001-111YA.

REFERENCES

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgment. *Nature, 393,* 470–474.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372,* 669–672.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., Anderson, A., Lee, G. P., & Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37,* 1111–1117.

Aggleton, J. P. (1992). *The amygdala. Neurobiological aspects of emotion, memory, and mental dysfunction.* New York: Wiley-Liss.

Akirav, I., & Richter-Levin, G. (1999). Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral

amygdala stimulation in the rat. *Journal of Neuroscience, 19,* 10530–10535.
Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia–thalamocortical circuits: Parallel substrates for motor, oculomotor, ''prefrontal'' and ''limbic'' functions. *Progress in Brain Research, 85,* 119–146.
Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The amygdala. Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 1–66). New York: Wiley-Liss.
Barbas, H., & De Olmos, J. (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *Journal of Comparative Neurology, 300,* 549–571.
Blair, R. J., Morris, J. S., Frith, C. D., Perrett, D. I., & Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain, 122,* 883–893.
Bowers, D., Blonder, L. X., Feinberg, T., & Heilman, K. M. (1991). Differential impact of right and left hemisphere lesions on facial emotion and object imagery. *Brain, 114,* 2593–2609.
Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., & Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17,* 875–887.
Büechel, C., & Friston, K. J. (1997). Characterising functional integration. In R. S. J. Frackowiak (Ed.), *Human brain function* (pp. 127–140). San Diego: Academic Press.
Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience, 21,* 294–299.
Campbell, R., Heywood, C. A., Cowey, A., Regard, M., & Landis, T. (1990). Sensitivity to eye gaze in prosopagnosic patients and monkeys with superior temporal sulcus ablation. *Neuropsychologia, 28,* 1123–1142.
Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience, 20,* RC99.
Canli, T., Zhao, Z., Desmond, J. E., Kang, E., Gross, J., & Gabrieli, J. D. (2001). An fMRI study of personality influences on brain reactivity to emotional stimuli. *Behavioral Neuroscience, 115,* 33–42.
Carmichael, S. T., & Price, J. L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *Journal of Comparative Neurology, 363,* 615–641.
Duvernoy, H. M. (1999). *The human brain. Surface, blood supply, and three-dimensional sectional anatomy*. Wien, Austria: Springer.
Elliott, R., & Dolan, R. J. (1998). Neural response during preference and memory judgments for subliminally presented stimuli: A functional neuroimaging study. *Journal of Neuroscience, 18,* 4697–4704.
Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cerebral Cortex, 10,* 308–317.
Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6,* 218–229.
Friston, K. J., Holmes, A. P., & Worsley, K. J. (1999). How many subjects constitute a study? *Neuroimage, 10,* 1–5.
Friston, K. J., Holmes, A. P., Worsely, K. J., Poline, J. P., Frith, C. D., & Frackwiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2,* 189–210.
Gaffan, D., Murray, E. A., & Fabre-Thorpe, M. (1993). Interaction of the amygdala with the frontal lobe in reward memory. *European Journal of Neuroscience, 5,* 968–975.
Gaffan, E. A., Gaffan, D., & Harrison, S. (1988). Disconnection of the amygdala from visual association cortex impairs visual reward-association learning in monkeys. *Journal of Neuroscience, 8,* 3144–3150.
Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, U.S.A., 96,* 8301–8306.
Goldman-Rakic, P. S., & Porrino, L. J. (1985). The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. *Journal of Comparative Neurology, 242,* 535–560.
Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., Pietrini, P., Wagner, E., & Haxby, J. V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience, 14,* 1450–1462.
Hariri, A. R., Bookheimer, S. Y., & Mazziotta, J. C. (2000). Modulating emotional responses: Effects of a neocortical network on the limbic system. *NeuroReport, 11,* 43–48.
Hasselmo, M. E., Rolls, E. T., & Baylis, G. C. (1989). The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. *Behavioral Brain Research, 32,* 203–218.
Hoffman, E. A., & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience, 3,* 80–84.
Iwai, E., & Yukie, M. (1987). Amygdalofugal and amygdalopetal connections with modality-specific visual cortical areas in macaques. *Journal of Comparative Neurology, 261,* 362–387.
Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., Ollinger, J. M., Akbudak, E., Conturo, T. E., Snyder, A. Z., & Petersen, S. E. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron, 20,* 927–936.
Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122,* 981–991.
Leonard, C. M., Rolls, E. T., Wilson, F. A., & Baylis, G. C. (1985). Neurons in the amygdala of the monkey with responses selective for faces. *Behavioral Brain Research, 15,* 159–176.
McDonald, A. J., Mascagni, F., & Guo, L. (1996). Projections of the medial and lateral prefrontal cortices to the amygdala: A *Phaseolus vulgaris* leucoagglutinin study in the rat. *Neuroscience, 71,* 55–75.
Morris, J. S., Friston, K. J., Buchel, C., Frith, C. D., Young, A. W., Calder, A. J., & Dolan, R. J. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121,* 47–57.
Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383,* 812–815.
Nakamura, K., Mikami, A., & Kubota, K. (1992). Activity of single neurons in the monkey amygdala during performance of a visual discrimination task. *Journal of Neurophysiology, 67,* 1447–1463.
Nishijo, H., Ono, T., & Nishino, H. (1988). Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. *Journal of Neuroscience, 8,* 3570–3583.
Ono, T., Nishijo, H., & Uwano, T. (1995). Amygdala role in

conditioned associative learning. *Progress in Neurobiology, 46,* 401–422.
Perrett, D. I., Smith, P. A., Potter, D. D., Mistlin, A. J., Head, A. S., Milner, A. D., Jeeves, M. A. (1985). Visual cells in the temporal cortex sensitive to face view and gaze direction. *Proceedings of the Royal Society of London, Series B: Biological Sciences, 223,* 293–317.
Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., Bullmore, E. T., Perrett, D. I., Rowland, D., Williams, S. C., Gray, J. A., & David, A. S. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature, 389,* 495–498.
Reuter-Lorenz, P., & Davidson, R. J. (1981). Differential contributions of the two cerebral hemispheres to the perception of happy and sad faces. *Neuropsychologia, 19,* 609–613.
Russell, J. A., & Bullock, M. (1985) Multidimensional scaling of emotional facial expressions: Similarity from preschoolers and adults. *Journal of Personality and Social Psychology, 48,* 1290–1298.
Sergent, J., & Bindra, D. (1981). Differential hemispheric processing of faces: Methodological considerations and reinterpretation. *Psychological Bulletin, 89,* 541–554.
Sprengelmeyer, R., Rausch, M., Eysel, U. T., & Przuntek, H. (1998). Neural structures associated with recognition of facial expressions of basic emotions. *Proceedings of the Royal Society of London, Series B: Biological Sciences, 265,* 1927–1931.
Stone, V. E., Nisenson, L., Eliassen, J. C., & Gazzaniga, M. S. (1996). Left hemisphere representations of emotional facial expressions. *Neuropsychologia, 34,* 23–29.
Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* Stuttgart: Thieme.
Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., & Koeppe, R. A. (1998). The effect of emotional content on visual recognition memory: A PET activation study. *Neuroimage, 8,* 188–197.
Ungerleider, L. G. (1995). Functional brain imaging studies of cortical mechanisms for memory. *Science, 270,* 769–775.
Whalen, P. J. Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18,* 411–418.
Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *NeuroReport, 12,* 379–383.
Young, A. W., Newcombe, F., de Haan, E. H., Small, M., & Hay, D. C. (1993). Face perception after brain injury. Selective impairments affecting identity and expression. *Brain, 116,* 941–959.