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Functional association of the amygdala and ventral prefrontal cortex during cognitive evaluation of facial expressions primed by masked angry faces: an event-related fMRI study

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The present study examined the functional association of the amygdala and right ventral prefrontal cortex (PFC) during cognitive evaluation of facial expressions. A situation was created where emotional valence of the stimuli was unconsciously manipulated by using subliminal affective priming. Twelve healthy volunteers were asked to evaluate the facial expressions of a target face (500-ms duration) such as "anger", "neutral", or "happy". All target faces expressed relatively weak anger. Just before the presentation of the target face, a prime of three conditions of 35-ms duration, angry face, neutral face, and white blank was presented. The subjects could not consciously identify the primes in this procedure. Activity in the right amygdala was greater with subliminal presentation of the angry prime compared with subliminal presentation of a neutral face or white-blank stimuli. Most importantly, the degree of activation of the right amygdala was negatively correlated with that of the right ventral PFC only with the anger prime. Furthermore, activation of the amygdala was positively correlated with rate of judgment when the subjects recognized anger in the target faces. These results are discussed in terms of the functional association between the right PFC and the amygdala and its influence on cognitive processing.

Keywords: Amygdala; Prefrontal cortex; fMRI study

Introduction

The interconnections between the amygdala, a subcortical structure known to be critical in emotional responses (Aggleton, 1992, 2000), and the prefrontal cortices (PFC), which are associated with various higher-level cognitive processing, are thought to play a major role in the integration of emotional and cognitive processes (Barbas, 2000). Hariri et al. (2000, 2003) have recently shown that the right PFC modulates activity of the amygdala during cognitive evaluation of emotional stimuli including facial expressions. Specifically, whereas perceptual processing (matching) of aversive emotional stimuli such as fearful and angry faces or fearful pictures robustly activated the amygdala bilaterally, a paired pattern of greater responses in the right PFC and attenuated responses in the amygdala was observed during cognitive processing (verbal labeling). Recently, further evidence has been reported on PFC–amygdala interactions in the cognitive processing of emotional stimuli (Keightley et al., 2003; Lange et al., 2003). Hariri et al. (2003) have argued that this phenomenon should reflect an adaptive ability that enables humans to control our primitive emotional responses through conscious evaluation.

On the other hand, some theorists have attributed superiority of emotional responses over conscious cognitive processes realized mainly by PFC to limbic structures including the amygdala (LeDoux, 1996, 2002; Zajonc, 1980). One rationale for the affective primacy hypothesis comes from the psychological finding that even subtle emotional signals sometimes can be unconsciously detected and can initiate emotional responses. For instance, Öhman (1992) demonstrated that skin conductance responses (SCRs) to facial expressions of anger conditioned to an aversive electric shock were evoked even when the stimuli were subliminally presented using a technique called backward masking. Additionally, presentation of masked angry faces of significant others decreased the subjects' self-esteem (Baldwin et al., 1990). These findings suggest that we can not necessarily identify the origins of emotions and sometimes be unaware of emotional responses evoked in ourselves. This can be thought of as evidence for discrepancy between "unconscious discrimination" and "overt recognition" in processing of a certain emotional stimulus (Tranel and Damasio, 1985). Whereas the PFC may play a major role in the overt recognition of an emotional stimulus, the unconscious discrimination or detection of the stimulus can be attributed to the amygdala. Indeed, recent neuroimaging studies have indicated that the amygdala is involved in the subliminal perception of fearful and angry faces (Whalen et al., 1998; Morris et al., 1998b), probably via a subcortical pathway to the amygdala, including

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the superior colliculus and pulvinar (Morris et al., 1999; Vuilleumier et al., 2003).

The purpose of the present study was to evaluate the interaction between the PFC and the amygdala during unconscious emotional processing, in comparison to conscious emotional processing examined by Hariri et al. (2000, 2003). Specifically, our main interest was whether modulation by the PFC over the amygdala, and the pattern of increased activity in the PFC with attenuated responses in the amygdala, can occur when an automatic or unconscious emotion is evoked by an unseen masked emotional signal. Cognitive evaluation is performed for an independent stimulus. We have especially focused on the right medial parts of the middle frontal and inferior frontal gyri because these areas are associated with response inhibition (Garavan et al., 1999; Konishi et al., 1999) and have a inhibitory control over the response of the amygdala (Beauregard et al., 2001; Iidaka et al., 2001; Nakamura et al., 1999; Narumoto et al., 2000; Nomura et al., 2003). Furthermore, we are interested in how the PFC–amygdala interaction contributes to overt recognition of the emotional stimulus.

The paradigm of subliminal affective priming (Murphy and Zajonc, 1993; Niedenthal, 1990; Murphy et al., 1995; Winkielman et al., 1997) provides a fine experimental tool for addressing these issues. Specifically, the paradigm of the present study consisted of two experimental and one control condition. Subjects had 500 ms to respond to either a facial expression of intense anger, an affectively neutral facial expression, or a blank-white screen as a control stimulus was randomly presented as a prime for 35 ms and masked by a low level of anger in the facial expression as a target (Fig. 1). The subjects were required to categorize the facial expressions as anger, neutral, or happy. Although previous studies (Hariri et al., 2000, 2003) have employed typical and prominent emotional stimuli (facial expressions and scenes), the current study utilizes faces showing relatively weaker anger as target stimuli. This was to prevent a ceiling effect in the accuracy of evaluation so as to compare influence of primes on subject evaluation. This technique can unconsciously manipulate emotional valences of a target stimulus, and can probably manipulate related activity in the amygdala without any changes in conscious perception about the target stimulus.

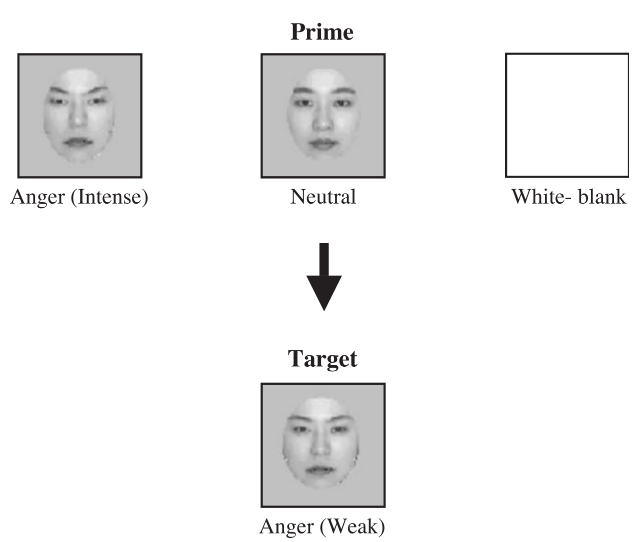

Fig. 1. Examples of primes in three conditions (top) and a target (bottom) are shown.

Brain activity was evaluated using event-related functional magnetic resonance imaging (fMRI). Unlike conventional block paradigms of fMRI, event-related scan acquisition should be especially useful in studies, including the present one, which require rigorous experimental manipulation, because event-related fMRI enables us to use trial-by-trial randomization of the conditions. However, event-related fMRI is thought to be inferior in its statistical power to the conventional block-design fMRI. We were unsure whether we could detect activation of small cerebral structures, such as the amygdala especially where amygdalar activity would be suppressed by the subliminal emotional prime following the cognitive evaluation task. Considering this, the present study employed a scan procedure with more spatial resolution within a relatively focused range including the amygdala and middle and inferior parts of PFC using relatively thin slices (2.0 mm). Thin slices has been reported useful in reducing the distortion artifacts (LaBar et al., 2001). To ensure an adequate signal-to-noise ratio, we removed low-frequency signal intensity drift in the preprocessing step (Iidaka et al., 2003).

Methods

This study consists of three phases: (i) development of stimuli, (ii) an fMRI experiment, and (iii) a manipulation check of subliminal presentation of prime. Different groups of subjects participated in the three phases.

Development of stimuli

Purpose and subjects

We used digitized grayscale pictures of the faces of five Japanese women showing intense anger or a neutral facial expression as primes in our fMRI and supplementary experiment for manipulation check. The target stimuli were images of faces of the women showing ambiguous weak anger. Fifteen female undergraduates [mean age = 21.5 years old, standard deviation (SD) = 1.9 years] conducted a task for developing the set of face stimuli.

Procedure

First, digitized images of 14 female undergraduates' faces showing neutral facial expressions were prepared. The images were processed using a morphing technique "Face tool version 4.0" (Morishima, 1996; Morishima et al., 1995), which is a computer program developed in Japan that has been used to synthesize facial expressions. For the 14 women, we produced images of facial anger with 10 levels (10–100%) of emotional intensity. Each face stimulus was shown to the subjects for 5 s on a screen through a PC projector. The subjects rated each facial expression from six scales of emotion (anger, sadness, happiness, surprise, fear, and disgust) of five levels of intensity (0: not at all–4: very intense). They also rated the naturalness of each facial expression with the same five levels (0: very unnatural–4: very natural). Based on the mean rating scores, we selected stimuli to be used in subsequent phases of the present study (an fMRI experiment and an experiment for manipulation check). The mean rating of the selected stimuli exceeded 2.0 with expressions of intense anger, and those of ambiguous expressions were within 0.8–1.5 on the anger scale. Additionally, ratings for the naturalness for all selected facial stimuli were more than 2.7. Evaluation of stimuli strength of other emotional expression was relatively low (less than

0.8). Through the above-mentioned procedure, combinations of intense and less-angry facial expressions, and neutral faces of five persons were established. Details of the procedure for the development of facial stimuli have been described elsewhere (Haneda et al., 2003).

fMRI experiment

Subjects

Nine right-handed undergraduate and graduate students (5 males, 5 females; mean age = 23.5; SD = 2.1) participated in the fMRI experiment. All subjects were healthy, with no past history of psychiatric or neurological illness and were not taking any medication. All subjects gave written informed consent to participate in the study. The Ethics Committee of Fukui Medical University approved this study.

Task procedure

According to a typical procedure of affective priming, presentation of a prime stimulus to which no overt response was required was followed by a target stimulus that had to be evaluated. Subjects were instructed to evaluate the emotion expressed by a target face as ''anger'', ''neutrality'', or ''happiness'' and to answer by pressing a key using their forefinger, middle finger, and ring finger on their right hands. Correspondence of responses and keys was randomized across the subjects. All of the target faces, of 500-ms duration, expressed weak anger. Because the intensity of their expression was subtle and ambiguous, discrimination of the targets' expression was difficult for the subjects. Just before presentation of the target face, one prime of three conditions was presented with duration of 35 ms. Thus, stimulus-onset-asynchrony of a prime and a target was fixed at 35 ms in each trial. Primes showed either intensely angry facial expressions (anger prime condition), neutral faces (neutral prime condition), or a white blank as a control stimulus (control condition).

Some previous neuroimaging studies investigating the neural correlates of processing of subliminally presented facial expressions (Morris et al, 1998b; Whalen et al., 1998) have used faces of different people in the combination of a prime and a target. However in the present study, the angry prime, the neutral prime condition, and any combination of primes a target were formed by using the same face images throughout the trials. We chose this manipulation because of perceptual factors. Generally, luminance and contrast are key factors for the effect of masking. We considered that differences in luminance and contrast of the prime and target would be minimized when face images of the same individual are used as the two stimuli. This would result in efficiently preventing a subject's conscious awareness of the prime. However, Whalen et al. (2001) have suggested that the face of a different individual is generally more efficient as a mask. Considering this, a rigorous examination of the validity of the masking effect of the same person's face was needed. Thus, we conducted a supplementary experiment to test whether a prime cannot be recognized with explicit awareness even when the face of the same individual as the prime is used as a mask (details of the experiment are described below).

Thirty trials in each condition were conducted with an inter-trial-interval (ITI) of 12 s. The order of stimulus presentation was randomized across subjects, and the total of 90 trials were divided into three runs and an intermission of a few minutes were positioned between runs to maintain subjects' motivation and concentration. Because a set of faces of five different individuals was used as stimuli, each individual's face was displayed six times as a target for each condition and six times for a prime in the anger prime and neutral prime conditions. The stimuli were generated on a personal computer and projected onto a half transparent screen by a LCD projector. The subjects observed the stimuli through a tilted mirror attached to the head coil of the scanner. The subjects' responses and reaction times (RTs) were recorded.

Image acquisition and analysis

Functional images were acquired in an axial orientation, covering 32 slices (2.0-mm thickness with 0-mm gap), beginning from the base of the temporal lobes upward to the superior part of thalamus, using a 3-T MRI system (GE, Milwaukee, USA) equipped with single shot EPI (TR = 2.0 s; TE = 30 ms; flip angle = 90°; field of view (FOV) = 220 mm; 64 × 64 matrix). After discarding the first six images, the subsequent 180 images for each run were analyzed. A T2-weighted anatomical image was also acquired. The functional images were realigned to the first images 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) using parameters obtained from the normalization process of the coregistered anatomical image to the MNI T2-weighted template. Finally, the images were smoothed by an 8-mm Gaussian kernel. The study was conducted at the Biomedical Imaging Research Center at Fukui Medical University.

For fMRI group data analysis, all images of all subjects were analyzed in one design matrix, generating a fixed effect model hemodynamic responses to the stimulus onset for each event type (anger, neutral, blank) were separately modeled with canonical hemodynamic response function (HRF). These functions were used as subject-specific regressors in a general linear model, together with a constant term and basis set of cosine functions to remove low-frequency drifts in the blood oxygenation level-dependent (BOLD) signal (Holmes et al., 1997). The parameter estimates pertaining to the height of the HRF for each event type regressor obtained from the least mean square fit of the model to the data were stored as separate contrast images. The signal was proportionally scaled in arbitrary units by setting the whole brain mean value to 100. We created contrast images for the main effect of the task for all conditions. In addition, contrast images for each of the two conditions, and for subtraction between anger and neutral conditions, were determined.

We had an a priori hypothesis about interactions between activation of the amygdala and PFC. Considering that the amygdala is a small neural structure and its activation might be relatively difficult to detect, the statistical threshold was set to $P < 0.005$ (uncorrected). Additionally, we also partially referred to regions activated with the lowest threshold ($P < 0.05$, uncorrected) in the context of the hypothesis. We believe that this less-conservative analysis might be permitted if the observed pattern of brain activation supports the hypothesis and that no activation of irrelevant brain areas to the hypothesis is detected. Clusters larger than seven contiguous voxels were reported. The peak heights and spatial extents of the resulting areas of activation were characterized. In particular, we are interested in investigating the regions specifically involved in the processing of the anger prime face by the subtraction of other conditions (neutral, control) from anger condition.

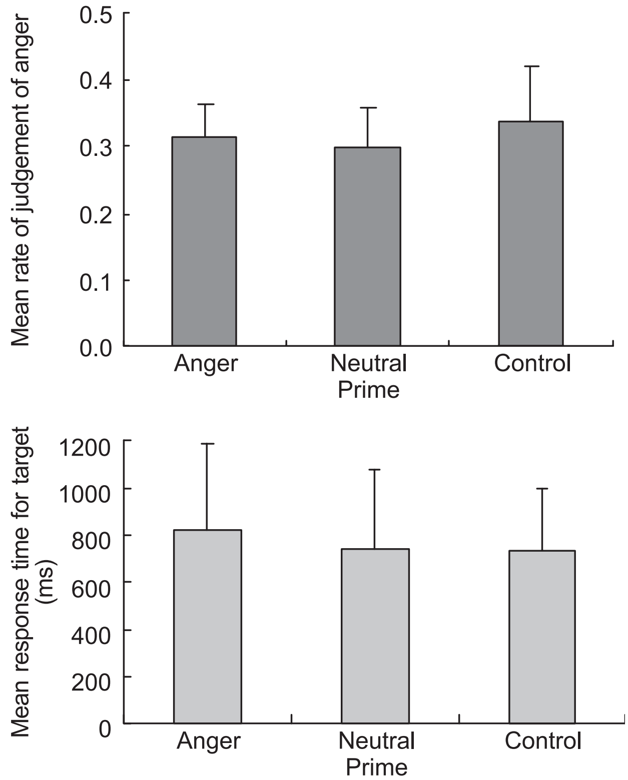

Fig. 2. Mean rate of judgment of anger for targets (top) and reaction time (bottom) in each condition. Error bars represent standard deviation.

Correlation analyses and structural equation modeling

The main purpose of the current study was to clarify the functional association of the amygdala with the PFC during cognitive evaluation of facial expressions. To determine the effects of prior unconscious manipulation of affective valence using subliminal affective priming, we conducted a series of correlation analyses. First, the correlation of the signal intensity in the peaks of the activation detected in the above-mentioned image analysis was examined in each condition. For these analyses of the BOLD signals, increases from the fixed baseline were extracted from the maximally activated voxels of regions detected in the statistical map in each condition. We did not seek to explore neural responses correlated with subliminal affective priming but we used the technique to examine the association of the amygdala with the PFC in unconscious emotion. However, we were interested in the influence of neural responses in both brain regions on evaluative processes. Thus, as a next step, we determined the correlation between behavioral data (categorization response for targets and RTs) and brain activity detected during image analysis in each condition.

Furthermore, to ascertain the causal relationship between the activity of the cerebral regions and behavioral data as a whole, for each condition, we performed analysis by structural equation modeling using AMOS software (version 4.01, SmallWaters, Chicago, IL, USA). Because we did not have an a priori causal model, we established a model from both image and correlation analysis. Adjusted signals from the image analysis that were derived from functional clusters in the right side of the amygdala, fusiform gyrus, and inferior frontal gyrus and behavioral data (rate of judgment of anger to target stimuli) were entered as variables. For each condition, goodness-of fit values, expressed as Comparative Fit Index, Tucker–Lewis Index (CFI, TLI), were determined. Several constraints were applied to the model: (i) the residual variances for every parameter were fixed at the observed variances divided by 4 to accomplish the stable results in the small number of the observations (n = 9), and (ii) the path coefficients from the residual variance to the observed variables were fixed at one (Büechel and Friston, 1997; Iidaka et al., 2001). The values of the estimated path coefficients were standardized.

Manipulation check for subliminal presentation of primes

Subjects

Ten male and ten female undergraduates (mean age = 21.0 years old; SD = 1.5 years) participated in this supplementary experiment.

Task procedure

The stimuli used in the fMRI experiment were presented in the same procedure as described above. The subjects were told that two different images would be presented in succession in each trial. They were further told that a facial expression of anger, a neutral face, or a blank would be presented very briefly just before a target

Table 1
Significant BOLD fMRI responses for primes and comparisons

	Talairach coordinates			
	(x, y, z)	Cluster size	Z score	
Basic condition				
Anger prime				
Fusiform gyrus (BA 37)	24, −58, −12	41	3.31	$P < 0.001$
Inferior frontal gyrus (BA 47)	48, 18, −10	5	2.58	$P < 0.003$
Amygdala	16, −6, −16	9	2.25	$P < 0.05$*
Neutral prime				
Inferior frontal gyrus (BA 47)	40, 20, −10	74	4.45	$P < 0.001$
Fusiform gyrus (BA 37)	26, −52, −12	16	3.60	$P < 0.003$
Control				
Fusiform gyrus (BA 37)	24, −25, −12	65	4.25	$P < 0.001$
Main effect of task				
Anger prime > control				
Amygdala	16, −8, −16	7	3.27	$P < 0.001$
Neutral prime > control				
Thalamus	−8, −18, −14	7	3.32	$P < 0.001$
Direct comparison				
Anger prime > neutral prime				
Amygdala	16, −8, −14	20	2.91	$P < 0.005$

Coordinates represent voxels in each region with most significant magnitude and spatial extent ($P < 0.005$, uncorrected).
BOLD, blood oxygen level dependent; fMRI, functional magnetic resonance imaging. BA, Broadmann's area.
* Lenient threshold ($P < 0.05$, uncorrected).

face. The task for the subjects was to judge which stimulus would be presented in each trial in a forced choice manner. In addition, they were required to rate confidence of their judgment in a five-point scale (1: not certain at all–5: very certain) in each trial.

Results

As no gender difference was shown in both behavioral and neuroimaging results, data from male and of female subjects were combined for analysis.

Manipulation check

The results of the supplementary experiment for the manipulation check indicated that the rate of correct judgment for each prime condition was at a chance level [χ^2 (2) < 0.47, ns] and the ratings of confidence were relatively low in each condition [mean ratings and SDs shown in parentheses; 1.25 (0.47), 1.34 (0.47), 1.23 (0.40), for the anger prime, neutral prime, and control conditions, respectively]. The rate of correct judgment was not significantly different between the male and female subjects [$F(1,18) = 0.45$, ns]. Furthermore on debriefing after the session of the fMRI experiment, no subjects showed explicit knowledge of the masked prime stimuli. These results confirmed that the prime stimuli were presented outside awareness of the subjects.

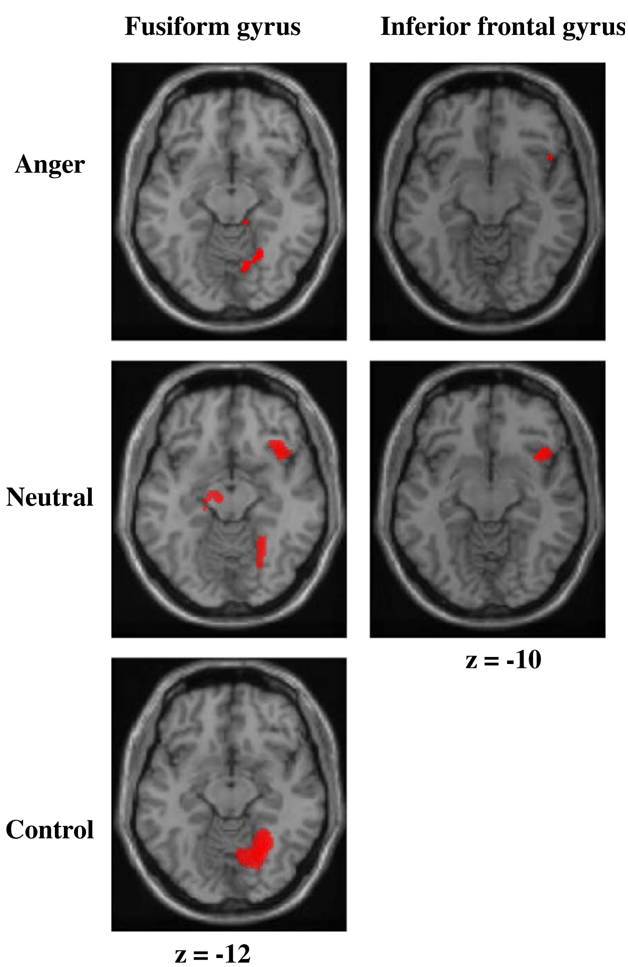

Fig. 3. Regions of the brain that were significantly activated in the anger prime condition (top), the neutral prime condition (middle), and the control condition (bottom) are shown. An uncorrected *P* value of 0.005 was used as the threshold. Activation in the right inferior frontal and right fusiform gyri is indicated.

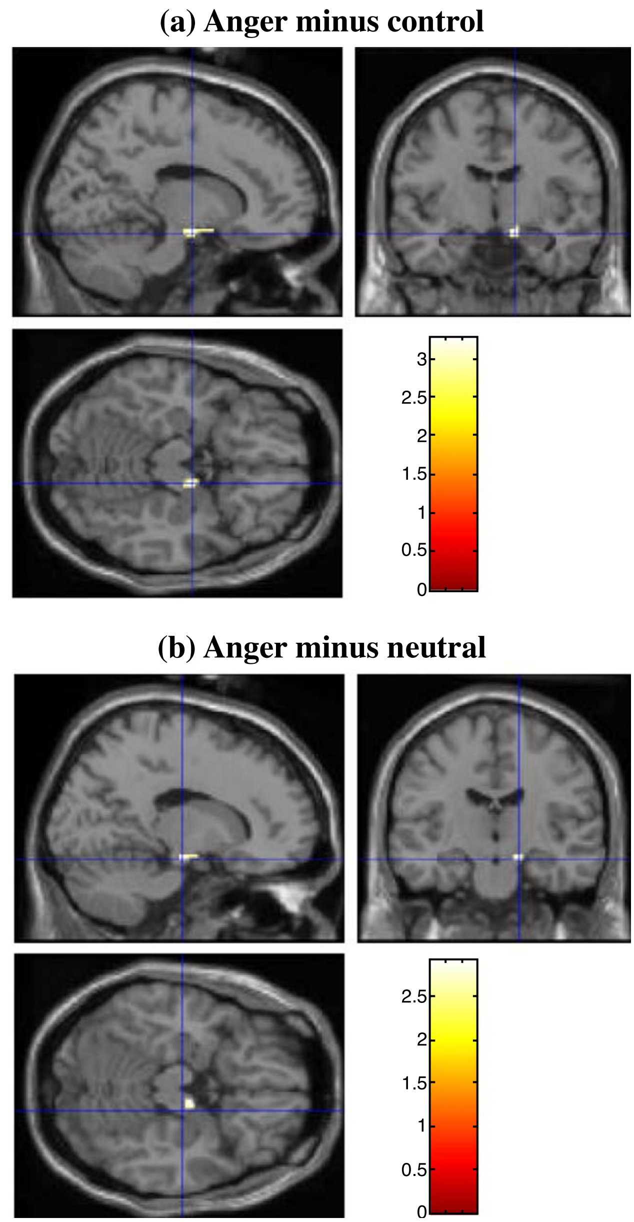

Fig. 4. Significantly activated brain regions determined as the net of the anger prime condition minus the control condition (top) and the anger prime condition minus the neutral condition (bottom). An uncorrected *P* value of 0.001 was used as the threshold. Activity in the right amygdala was significantly greater in the anger prime condition than in the control and the neutral prime conditions.

Behavioral data

The rate of judgment of anger for target stimuli and the reaction time in the task showed no statistically significant difference between the three conditions [$F(3,27) = 0.37$, ns, $F(3,27) = 0.14$, ns, respectively; Fig. 2]. The rate of judgment of anger for

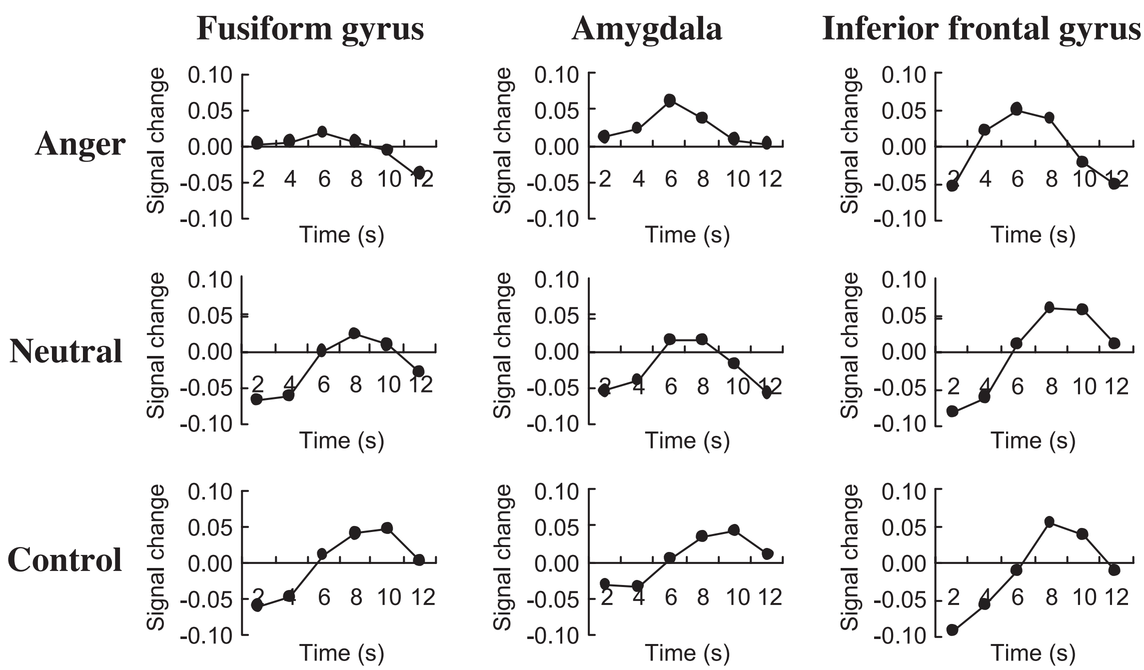

Fig. 5. Variations in the time course of BOLD signals in the anger prime condition (top), the neutral prime condition (middle), and the control condition (bottom).

target stimuli and the reaction time were not different between the male and female subjects [$F(1,7) = 0.68$, ns; $F(1,7) = 0.34$, ns). The results indicated that prior subliminal presentation of intense angry faces did not influence subsequent conscious evaluation of the target faces.

Imaging data

First, we identified brain regions showing significant changes in the regional blood oxygenation level-dependent (BOLD) activity in each condition (basic conditions in Table 1). Robust activation in the right fusiform gyrus was observed in each condition ($P < 0.001$, uncorrected; Fig. 3 and Table 1). Additionally, significant activation of the right ventral PFC area (inferior frontal gyrus) was observed with the anger prime and neutral prime conditions ($P < 0.005$, uncorrected; Fig. 3 and Table 1). In control conditions, activation of the right ventral PFC was found with the lowest statistical threshold [$P < 0.05$; coordinates of maximum = (x, y, z) = (38, 22, −12)]. Furthermore, in the separate analysis of the basic conditions, activation in the right amygdala was observed only with the anger prime condition [coordinates of maximum = (x, y, z) = (16, −6, −16), z = 2.33] with the lowest threshold ($P < 0.05$), but not in the neutral prime and control conditions.

We then identified the regions of the brain significantly activated as a result of the main effect of prime (anger prime vs. control and neutral prime vs. control). The contrast of the anger prime minus control revealed significant activation of the right amygdala [coordinates of maximum = (x, y, z) =(17, −8, −16), z = 3.29; $P < 0.001$, uncorrected; Fig. 4 and Table 1]. In contrast to the neutral prime minus control, significant activation was observed in the thalamus but not in the amygdala. No area with significant activation was found in the comparison of the control minus anger prime with the

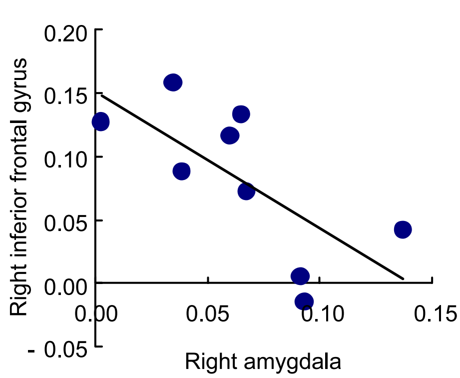

Fig. 6. Plots and regression lines of the correlation between the signal changes in brain regions in the anger prime condition. x-axis represents mean signal change in the right amygdala, and y-axis represents mean signal change in the right inferior frontal gyrus.

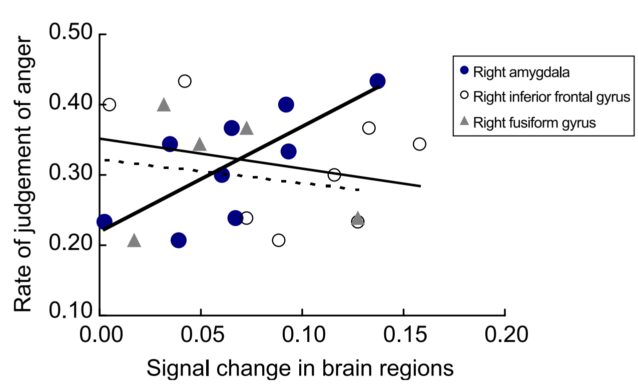

Fig. 7. Plots and regression lines of correlations between neural activity in the brain regions and rate of judgment of anger for target stimuli in the anger prime condition. Correlations between rate of judgment of anger and signal change in the right amygdala (bold line), in the right inferior frontal gyrus (dashed line), and in the right fusiform gyrus (dotted line) are shown.

control minus neutral prime. Direct comparison of the anger prime minus the neutral prime revealed significant activation in the right amygdala [coordinates of maximum = $(x, y, z) = (17, -8, -14)$, $z = 2.91$; $P < 0.005$, uncorrected; Fig. 4 and Table 1].

In the present study, an ITI of 12 s was used for presentation of stimuli, whereas some previous event-related fMRI studies on the amygdala activation used longer ITIs (e.g. 16 s in Canli et al., 2000). We adopted a relatively shorter ITI to maintain the subjects' concentration and motivation to the task; however, we needed to verify that BOLD signals can return to baseline. For this purpose, variation in the time course of the BOLD signal in the inferior frontal and fusiform gyri and amygdala were examined. The results revealed that the BOLD signals in each area returned to the baseline with an ITI of 12 s (Fig. 5). In our study, a total of five different faces were each displayed six times for a total of 30 trials. To examine the possibility of habituation effects resulting from repeated presentation of the stimuli, we compared a mean peak value of BOLD signal in the earlier half (45 trials) with that in the latter half (45 trials) of the total 90 trials. For this, we determined the peak value of the BOLD signal, during an ITI of 12 s for each trial, for each brain area reported above (the amygdala, inferior frontal gyrus, and fusiform gyrus). We observed no significant

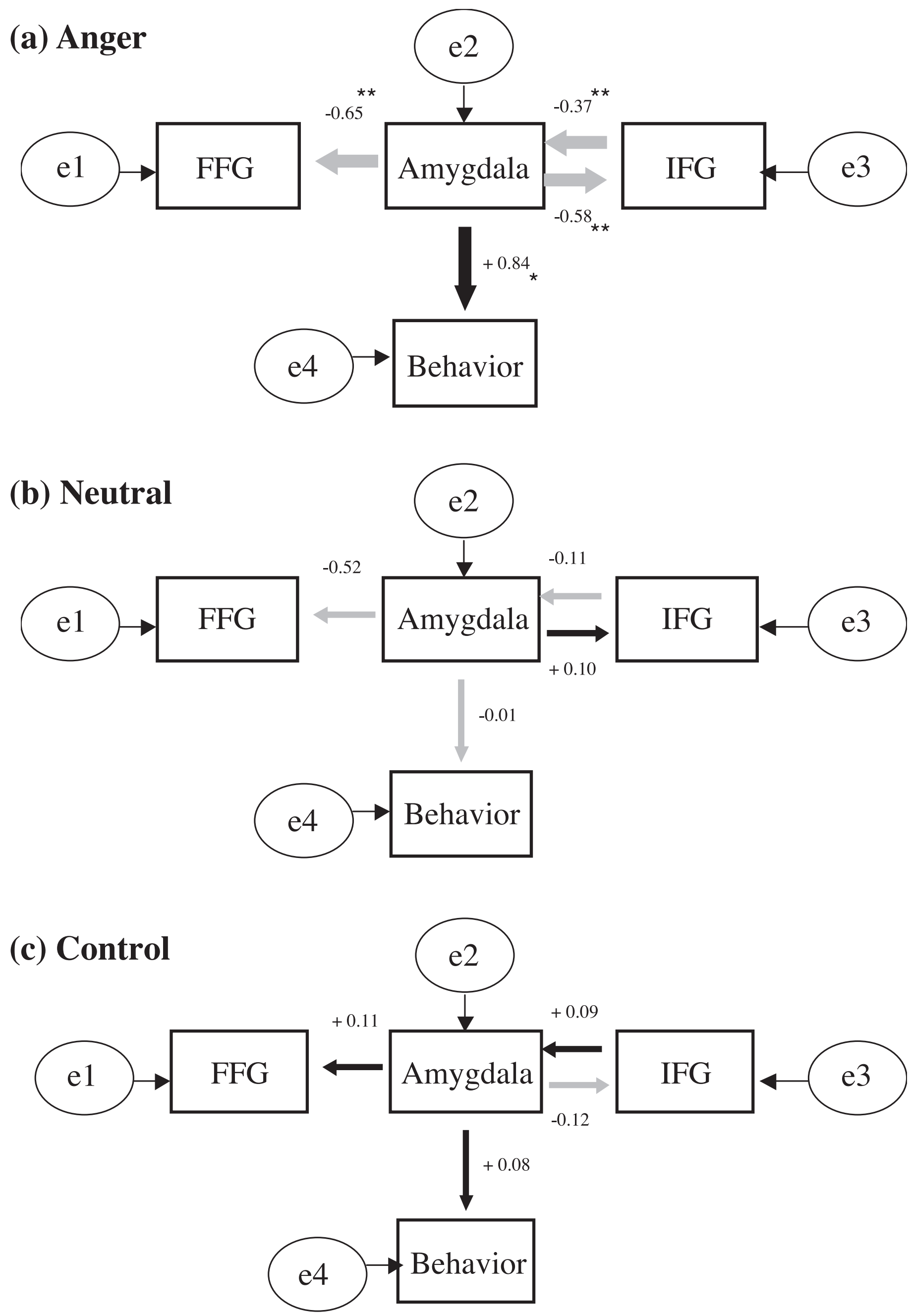

Fig. 8. Path diagram forms the analysis using structural equation modeling involving the right amygdala (Amygdala), right fusiform gyrus (FFG), right inferior frontal gyrus (IFG), and rate of judgment of anger (Behavior). The values of the standardized path coefficients under the anger, neutral condition, and control are indicated in (a), (b), and (c) respectively. Pathways representing a negative influence are diagonally striped. $*P < 0.05$; $**P < 0.01$.

difference between values in the earlier and latter half of the experiment in each area of the brain [the anger prime condition—the amygdala: t (8) = 1.83, ns; inferior frontal gyrus: t (8) = 2.31, ns; fusiform gurus: t (8) = −0.71, ns; the neutral prime condition—the amygdala: t (8) = 1.67, ns; inferior frontal gyrus: t (8) = 2.01, ns; fusiform gurus: t (8) = 1.04, ns; the control condition—the amygdala: t (8) = 1.33, ns; inferior frontal gyrus: t (8) = 1.56, ns; fusiform gurus: t (8) = 0.87, ns]. These results indicate habituation effects were not found.

Correlation analysis

For correlation analysis, the BOLD signals were extracted from the maximally activated voxels of the right inferior frontal and fusiform gyri in the statistical map for each condition. The BOLD signal for the right amygdala was extracted from the maximally activated voxel observed in the mail effect analysis of the anger prime versus control conditions. The results revealed a highly significant negative correlation between responses in the right amygdala with the responses in the right inferior frontal gyrus with the anger prime condition ($r = -0.70$, $P < 0.05$). Fig. 6 shows plots of relative signal changes in the right amygdala and right inferior frontal gyrus. No significant correlation was found between responses in right amygdala and in the right fusiform gyrus in the anger prime condition ($r = -0.31$, ns). No significant correlation was found in any combinations of the regions in either of the other two conditions.

How the brain regions involve overt recognition of facial expressions was one of our main interests. Thus, we determined whether correlations existed in each condition, between behavioral data (categorization response for targets and RT) and brain activity in the above-mentioned three cerebral regions (the right amygdala, inferior frontal gyrus, and fusiform gyrus). A significant positive correlation between the rate of judgment of anger and activation intensity in the right amygdala was observed only in the anger prime condition ($r = .74$, $P < 0.05$; Fig. 7). This result implies an influence of the amygdala on overt recognition of facial expression, and that the greater level of amygdala activation by a subliminal anger prime, the more likely a target face was judged as expressing anger. Activation in the right inferior frontal and fusiform gyri did not correlate with the judgment data. Additionally, RT showed some negative correlation with activation intensity in the right amygdala in the anger prime condition, although it was not statistically significant ($r = -.65$, $P < 0.10$). No correlation was found between brain activity and behavioral datum in the neutral prime and control conditions.

Structural equation modeling

Single correlation analysis suggest a functional association between the right amygdala and right PFC and the influence on cognitive evaluation only in the condition where emotional valence was unconsciously strengthened. For structural equation modeling, we established a causal model using the data of anger judgment and the activation scores in the right amygdala, the right PFC gyrus, and the right fusiform gyrus (Fig. 8). Good fitness of the model to the observed variance–covariance structure in each condition was determined (the anger prime condition: CFI = 1.00, TLI = 1.03; the neutral prime condition: CFI = 0.89, TLI = 0.85; the control condition: CFI = 0.92, TLI = 0.87). We predicted reciprocal paths between the amygdala and PFC on the basis of the hypothesis described in the introduction section. In the anger prime condition (Fig. 8a), significant mutual negative paths between the amygdala and the PFC were observed ($P < 0.01$), with a larger coefficient in the path from the amygdala to the PFC than in the reversed direction. A significant negative influence from the amygdala to the fusiform gurus was also found ($P < 0.01$). Additionally, it was clarified that activation in the right amygdala was involved in higher recognition of the target facial expressions as anger ($P < 0.05$). The activity in other brain regions did not directly influence cognitive evaluation of the target stimuli. In the two other conditions, any causal relationship between the parameters was not determined (Figs. 8b,c).

Discussion

In the present study, the subjects were subliminally presented with one of two types of prime (anger, neutral) and a control stimulus followed by a supraliminal target stimulus of faces showing a lower level of anger that required categorization. Most importantly, consistent with previous studies by Hariri et al. (2000, 2003), the response of the right amygdala was inversely correlated with that of the right inferior frontal gyrus during cognitive labeling of facial expressions only when unconscious emotional responses were evoked by subliminal presentation of intense angry faces. The peak of activation in the right inferior frontal gyrus observed in the anger prime condition (x, y, z = 48, 18, −10; Table 1) was in the ventral area of PFC (BA 47). Near the peak of activation, Hariri et al. (2003) found both during perceptual (Matching) and cognitive (Labeling) processing of emotional stimuli (x, y, z = 45, 18, −5). Therefore, our results, in agreement with previous studies, implicate modulation of the ventral PFC over the amygdala.

One merit of the present study might be that causes of engagement in the amygdala and the ventral PFC could be dissociated by adopting the technique of subliminal affective priming. The right amygdala might be unconsciously activated by the masked intensely angry faces but not by target faces expressing a lower level of anger, because activation of the amygdala was not observed in the control condition without any primes even with the lowest statistical threshold ($P < 0.05$). Also, its activation was not found in the neutral prime minus control conditions. The right ventral PFC was presumably engaged in the conscious cognitive evaluation of the target faces but not of the unseen primes, because the latter stimuli could not be perceived with awareness and thus could not initiate conscious processing. Indeed, it has been reported that the right side of ventral PFC including the inferior is activated during overt recognition or judgment of faces and facial expressions (Nakamura et al., 1999; Narumoto et al., 2000). Collectively, the function of the amygdala might relate to unconscious discrimination, and that the PFC might relate to the overt recognition step in the theoretical framework of Tranel and Damasio (1985) during processing of emotional facial expressions. The reversed correlation between responses in the right amydgala and in the ventral PFC observed in such a situation suggests an association of these two regions. Also, the right ventral PFC can modulate activity of the amygdala even when emotional responses in the amygdala are implicitly evoked by emotional signals independent of current conscious cognitive processing.

Interestingly, the results of the structural equation modeling indicated not only modulation effects of the right ventral PFC over the amygdala but also an influence in the opposite direction from activation of the amygdala to the right ventral PFC. Indeed, the path coefficient from the right amygdala to the right PFC (−0.58) was larger than that from the PFC to the amygdala (−0.37) in the anger prime condition (Fig. 8a). This might imply affective primacy over elaborative cognitive processing argued by Zajonc (1980) and LeDoux (1996, 2002). Although the structural equation modeling was not performed in the previous studies (Hariri et al., 2000, 2003), we speculate that the size of modulation effects might be larger in the path from the ventral PFC to the amygdala than in the opposite direction. Similarly, the influence from the amygdala to the ventral PFC might be diminished when facial expressions are presented supraliminally and the stimuli are consciously processed. A direct comparison between the functional association of the PFC and the amygdala in a subliminal situation with that in a supraliminal situation awaits future examination.

We have also shown that performance of cognitive evaluation for facial expressions can be influenced by balancing activation intensity of the amygdala with that of the ventral PFC. Correlation analysis and the structural equation modeling clearly provided evidence for a relationship between the responses in the amygdala and categorization of target facial expression in the condition where the subjects were primed by angry faces: the rate of judgment of anger was positively related to activity in the right amygdala. This finding implies that the affective priming effect of prior subliminal facial expressions could be associated with the degree to which the right amygdala participates in subsequent cognitive processing. Individuals who exhibit prominent activation in the right amygdala when they receive a subtle (subliminal) emotional signal with negative valence might tend to evoke implicit emotional responses and unconsciously utilize the inner emotional representation as a cue to interpret current stimuli. This might result in an increased possibility to interpret the current stimuli in congruent ways with their emotional states. Indirect support for this speculation can be obtained from the negative correlation between the activation of the amygdala and RT. Although it did not reach statistical significance because of the limited number of samples, it suggests that higher activation in the amygdala might lead to faster, and probably heuristic-based judgments using inner emotional representation as a cue such as affective priming (Forgas, 1995). On the opposite side of the continuum, individuals who show suppressed activity in the right amygdala, presumably by modulation of the right ventral PFC, tend to resist temptation for judgment relying on emotional heuristic-based judgments and engage in more elaborative and deliberative processing of current stimuli on the basis of online-input information from the stimuli. It has been widely argued that the right ventral PFC is involved with inhibition of responses (Garavan et al., 1999; Konishi et al., 1999). The present findings might, by showing that the brain area also works to inhibit emotional drives to responses even when we cannot be aware of its existence, expand the general understanding of inhibition functions in this region.

Recently, Hariri et al. (2002a) demonstrated that genetic variation in the serotonin transporter relates to the varied response of the amygdala to emotional stimuli; specifically, individuals with one or two copies of the short allele of the serotonin transporter promoter polymorphism exhibited greater neural activation in the amygdala in response to fearful stimuli compared with individuals with the long allele. We thus speculate that such genetic variation relating to functions of the amygdala and PFC might provide the biological basis for individual differences in the amygdala–ventral PFC functional balance during cognitive processing of emotional stimuli.

It needs to be noted that the mean rates of judgment of the target faces showing anger and RT for the judgment did not differ within the conditions. However, activation of the amygdala was detected in the anger prime minus the other conditions. Also, activation of the amygdala was predictive of anger discrimination during the anger prime condition. These results suggest a discrepancy in the processes of unconscious discrimination and overt recognition of exogenous emotional stimuli including facial expressions, and imply that the amygdala is involved in the former but not necessarily in the latter process. Indeed, the verbal labeling of facial expressions produced no localized activation in the amygdala (Hariri et al., 2000) and patients with amygdala lesions can report generally normal hedonic ratings of affectively valenced stimuli (Adolphs and Tranel, 1999). Without amygdala recognition, evaluation of emotional stimuli might be possible by a neural network including the frontal area (orbitofrontal cortex and anterior cingulate cortex), occipitotemporal cortex, and basal ganglia (for a review, see Adolphs, 2002). However, subjects with a bilateral amygdala lesion showed generally biased rating stimuli as less aversive than healthy control subjects (Adolphs and Tranel, 1999). Taken together, we interpret the positive correlation of the activation of the amygdala and judgment of anger in target faces as representing a relatively subtle biasing or modulation function of the amygdala over the overt recognition process performed in other areas of the brain.

The present results showed that the changes in the BOLD signal in the amygdala was significantly larger in the right but not left side with the anger prime condition compared to the other conditions. This result is consistent with a hypothesis presented by Morris et al. (1998b) that the right amygdala is more involved in the unconscious detection of meaningful stimuli, whereas the left amygdala is related to the conscious processing of emotional stimuli. However, there are some findings inconsistent with this notion: the observation of bilateral amygdalar activation both during subliminal with viewing of masked facial expressions (Whalen et al., 1998) and during conscious processing of faces (Hariri et al., 2000). Recently, an alternative model for laterality of amygdalar function suggested cognitively learned fear depends more on the left amygdala and experientially learned fear depends more on the right amygdala (Funayama et al., 2001; Phelps et al., 2001). This hypothesis of laterality can be interpreted also in a framework of top down (cognitively mediated: left) vs. bottom up (sensory driven: right) processing (Zald, 2003). Recent finding by Hariri et al. (2002b) that involvement of the right amygdala was more dominant during matching of facial expressions than during matching complex aversive visual scenes also supports the above notion: the right amygdala might be critical in processing the inherent emotional content of stimuli whereas the opposite side might involve in more cognitive nature of processing those stimuli. Additionally, the right amygdala showed more rapid habituation to fearful stimuli than the left amygdala, especially during processing of facial expressions (Hariri et al., 2002b), suggesting that the right amygdala might have a shorter time constant and might exhibit more transient responses than the left amygdala (Phillips et al., 2001; Write et al., 2001). Considering these arguments, we speculate that activation in the right but not left amydgala was observed in the present study because responses to the subliminal anger primes of short duration were not mediated by cognitive processes, but were driven totally by sensory input probably through thalamic nuclei (Morris et al., 1999; Vuilleumier et al., 2003), and evoked relatively transiently.

An unpredicted result in the structural equation modeling was the negative correlation between amygdalar activity and activation of the fusiform gyrus. The fusiform gyrus is an extrastriate visual area and is the suggested functional and anatomical homolog of the inferior temporal cortex of primates, which possesses a group of neurons related to structural encoding of faces (Perrett et al., 1982; Yamane et al., 1988). Recent human neuroimaging studies have reported robust activation in the fusiform gyrus during face recognition (Chao et al., 1999; Narumoto et al., 2001). According to Vuilleumier et al. (2001), the right side of the fusiform gyrus is more sensitive to emotional facial expressions than to emotionally neutral faces. The peaks of activation in this region were observed in the three basic conditions (anger prime, neutral prime, and control). Recent studies previously reported the face area of the fusiform gyrus (FFA; Allison et al., 1994; Kanwisher et al., 1997; Puce et al., 1995). It has been generally reported that activation of the amygdala can potentiate responses of the sensory areas including the fusiform gyrus through positive feedback projections (Amaral et al., 1992), especially during the processing of negative emotional information (Morris et al., 1998a; Tabert et al., 2001). Therefore, the present results showing the negative relationship between the amygdala and fusiform gyrus was not predicted. At the present time, this issue is difficult to resolve because no previous study has directly examined the amygdala–fusiform association during the unconscious processing of emotional information. One of the possible explanations is that this negative correlation might be related to the potentiation of amygdalar activity through a fast, subcortical route including the thalamic nuclei and suppression of cortical (e.g. PFC and fusiform gyrus) inputs by subliminal emotional signals. Unfortunately, the range of the scan in the present study did not cover the core parts of thalamus such as superior colliculus and pulvinar involved in direct input to the amygdala. Thus, this issue remains open to future research.

Anatomical neural architecture underlying the functional amygdala–ventral PFC interconnectivity is not fully understood. The majority of the direct reciprocal connections are found between the orbital PFC and the amygdala (Amaral et al., 1992; Barbas and De Olmos, 1990). Additionally, the amygdala has dense connections with the rostral part of the ACC (Bush et al., 2000; Devinsky et al., 1995). Thus, other PFC regions such as the ventral or dorsal PFC might indirectly interact with the amygdala probably via reciprocal projections to the orbital PFC or ACC. In this study, signals in the orbital PFC were not detected and the technical parameters for scanning did not allow for coverage of most regions in the ACC. Future studies should clarify the specific roles of the ventral and orbital PFC, and ACC in modulation of the amygdala.

One may criticize the present findings that the observed association between neural activities and behavioral performance during priming of angry faces might represent not emotional, but perceptual responses. Specifically, because faces of the same identities were used both for the intense angry prime and for the weak-angry target, similarity in the configuration of both images might cause repetitive priming (Henson et al., 2000; James et al., 1999) and may result in the neural activity observed in this study. Indeed, the repetitive priming effects have been observed in studies using face stimuli (Henson et al., 2000, 2002; Jiang et al., 2000) and in studies using subliminally presented stimuli (Dehaene et al., 2001; Naccache and Dehaene, 2001). However, the effects of perceptual repetition priming emerge with reduction in the activity of neural regions, especially visual areas in all studies cited above. In contrast to these findings, the current data indicates that the amygdala did show a differentiated pattern of activity with the anger prime and in the neutral prime conditions, where the same identities' faces were commonly presented as primes, increasing activity by the anger primes and unchanging activity with the neutral primes. Furthermore, the fusiform gyrus that has often been reported to indicate typical perceptual repetition priming did not show any effect of the primes in the present study. Taken together, changes in neural activity we show here may involve with not only perceptual or semantic but also emotional responses.

In conclusion, the current findings confirm that bidirectional modulation between the right ventral PFC and the amygdala can work in situations where emotional responses are evoked unconsciously. Furthermore, the functional balance of the amygdala–right ventral PFC might determine the degree that the inner emotional states influence current cognitive judgment.

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References

Adolphs, R., 2002. Neural systems for recognizing emotions. Curr. Opin. Neurobiol. 12, 169–177.

Adolphs, R., Tranel, D., 1999. Preferences for visual stimuli following amygdala damage. J. Cogn. Neurosci. 11, 610–616.

Aggleton, J.P., 1992. The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Wiley-Liss, New York.

Aggleton, J. (Ed.), 2000. The Amygdala: A Functional Analysis. Oxford Univ. Press, New York.

Allison, T., Ginter, H., McCarthy, G., Nobre, A.C., Puce, A., Luby, M., Spencer, D.D., 1994. Face recognition in human extrastriate cortex. J. Neurophysiol. 71, 821–825.

Amaral, D.G., Price, J.L., Pitkanen, A., Carmichael, S.T., 1992. Anatomical organization of the primate amygdaloid complex. In: Aggleton, J.P. (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction. Wiley-Liss, New York, pp. 1–66.

Baldwin, M.W., Carrell, S., Lopez, D.F., 1990. Priming relationship schemas: my advisor and the Pope are watching me from the back of my mind. J. Exp. Soc. Psychol. 26, 435–454.

Barbas, H., 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res. Bull. 52, 319–339.

Barbas, H., De Olmos, J., 1990. Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. J. Comp. Neurol. 300, 549–571.

Beauregard, M., Levesque, J., Bourgouin, P., 2001. Neural correlates of conscious self-regulation of emotion. J. Neurosci. 21, RC165.

Büechel, C., Friston, K.J., 1997. Characterising functional integration. In: Frackowiak, R.S.J. (Ed.), Human Brain Function. Academic Press, San Diego, pp. 127–140.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J.D.E., Cahill, L., 2000. Event-related activation in the human amygdala associates with later memory for individual emotional experience. J. Neurosci. 20, RC99.

Chao, L.L., Martin, A., Haxby, J.V., 1999. Are face-responsive regions selective only for faces? NeuroReport 10, 2945–2950.

Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., Riviere, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. Nat. Neurosci. 4, 678–680.

Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behavior. Brain 118, 279–306.

Forgas, J.P., 1995. Mood and judgment: the Affect Infusion Model (AIM). Psychol. Bull. 116, 39–66.

Funayama, E.S., Grillon, C., Davis, M., Phelps, E.A., 2001. A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. J. Cogn. Neurosci. 13, 721–729.

Garavan, H., Ross, T.J., Stein, E.A., 1999. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc. Natl. Acad. Sci. U. S. A. 96, 8301–8306.

Haneda, K., Nomura, M., Iidaka, T., Ohira, H., 2003. Interaction of prime and target in the subliminal affective priming effect. Percept. Mot. Skills 96, 695–702.

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.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R., 2002a. Serotonin transporter genetic variation and response of the human amygdala. Science 297, 400–403.

Hariri, A.R., Tessitore, A., Matty, V.S., Fera, F., Weinberger, D.R., 2002b. The amygdala response to emotional stimuli: a comparison of faces and scenes. NeuroImage 17, 317–323.

Hariri, A.R., Mattay, V.S., Tessitore, A., Fera, F., Weinberger, D.R., 2003. Neocortical modulation of the amygdala response to fearful stimuli. Biol. Psychiatry 53, 494–501.

Henson, R., Shallice, T., Dolan, R., 2000. Neuroimaging evidence for dissociable forms of repetition priming. Science 287, 1269–1272.

Henson, R.N., Shallice, T., Gorno-Tempini, M.L., Dolan, R.J., 2002. Face repetition effects in implicit and explicit memory tests as measured by fMRI. Cereb. Cortex 12, 178–186.

Holmes, A.P., Josephs, O., Buchel, C., Friston, K.J., 1997. Statistical modeling of low frequency confounds in fMRI. NeuroImage 5, S480.

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., Sadato, N., 2001. Neural interaction of the amygdala with prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. J. Cogn. Neurosci. 13, 1035–1047.

Iidaka, T., Terashima, S., Yamashita, K., Okada, T., Sadato, N., Yonekura, Y., 2003. Dissociable neural responses in the hippocampus to the retrieval of facial identity and emotion: an event-related fMRI study. Hippocampus 13, 429–436.

James, T.W., Humphrey, G.K., Gati, J.S., Menon, R.S., Goodale, M.A., 1999. Repetition priming and the time course of object recognition: an fMRI study. NeuroReport 10, 1019–1023.

Jiang, Y., Haxby, J.V., Martin, A., Ungerleider, L.G., Parasuraman, R., 2000. Complementary neural mechanisms for tracking items in human working memory. Science 287, 643–646.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. 17, 4302–4311.

Keightley, M.L., Winocur, G., Graham, S.J., Mayberg, H.S., Hevenor, S.J., Grady, C.L., 2003. An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. Neuropsychologia 41, 585–596.

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.

LaBar, K.S., Gitelman, D.R., Mesulam, M.-M., Parrish, T.B., 2001. Impact of signal-to-noise on functional MRI of the human amygdala. NeuroReport 12, 3461–3464.

Lange, K., Williams, L.M., Young, A.W., Bullmore, E.T., Brammer, M.J., Williams, S.C., Gray, J.A., Phillips, M.L., 2003. Task instructions modulate neural responses to fearful facial expressions. Biol. Psychiatry 53, 226–232.

LeDoux, J.E., 1996. The emotional brain: the mysterious underpinnings of emotional life. Simon and Schuster, New York.

LeDoux, J.E., 2002. Synaptic Self. Viking, New York.

Morishima, S., 1996. Modeling of facial expression and emotion for human communication system. Int. J. Disp. 17, 15–25.

Morishima, S., Kawakami, F., Yamada, H., Harashima, H., 1995. A modeling of facial expression and emotion for recognition and synthesis symbiosis of human and artifact. Future Comput. Des. Hum. Comput., 251–256.

Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J., 1998a. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 121, 47–57.

Morris, J.S., Öhman, A., Dolan, R.J., 1998b. Conscious and unconscious emotional learning in the human amygdala. Nature 393, 467–470.

Morris, J.S., Öhman, A., Dolan, R.J., 1999. A subcortical pathway to the right amygdala mediating "unseen" fear. Proc. Natl. Acad. Sci. U. S. A. 96, 1680–1685.

Murphy, S.T., Zajonc, R.B., 1993. Affect, cognition, and awareness: affective priming with optimal and suboptimal stimulus exposures. J. Pers. Soc. Psychol. 64, 723–739.

Murphy, S.T., Monahan, J.L., Zajonc, R.B., 1995. Additivity of nonconscious affect: combined effects of priming and exposure. J. Pers. Soc. Psychol. 69, 589–602.

Naccache, L., Dehaene, S., 2001. The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. Cereb. Cortex 11, 966–974.

Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Nagumo, S., Kubota, K., Fukuda, H., Kojima, S., 1999. Activation of the right inferior frontal cortex during assessment of facial emotion. J. Neurophysiol. 82, 1610–1614.

Narumoto, J., Yamada, H., Iidaka, T., Sadato, S., Fukui, K., Itoh, H., Yonekura, Y., 2000. Brain regions involved in verbal or non-verbal aspects of facial emotion recognition. Neuroreport. 11, 2571–2576.

Narumoto, J., Okada, T., Sadato, N., Fukui, K., Yonekura, Y., 2001. Attention to modulate fMRI activity in human right superior temporal sulcus. Brain Res. Cogn. Brain Res. 12, 225–231.

Niedenthal, P.M., 1990. Implicit perception of affective information. J. Exp. Soc. Psychol. 26, 505–527.

Nomura, M., Iidaka, T., Kakehi, K., Tsukiura, T., Hasegawa, T., Maeda, Y., Matsue, Y., 2003. Frontal lobe networks for effective processing of ambiguously expressed emotions in humans. Neurosci. Lett. 348, 113–116.

Öhman, A., 1992. Fear and anxiety as emotional phenomena: clinical phenomenology, evolutionary perspectives, and information-processing mechanisms. In: Lewis, M., Haviland, J.M. (Eds.), Handbook of Emotion. Guilford, New York, pp. 511–536.

Perrett, D.I., Rolls, E.T., Caan, W., 1982. Visual neurons responsive to faces in the monkey temporal cortex. Exp. Brain Res. 47, 329–342.

Phelphs, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of gear. Nat. Neurosci. 4, 437–441.

Phillips, M.L., Medford, N., Young, A.W., Williams, L., Williams, S.C., Bullmore, E.T., Gray, J.A., Brammer, M.J., 2001. Time courses of left and right amygdalar responses to fearful facial expressions. Hum. Brain Mapp. 12, 193–202.

Puce, A., Allison, T., Gore, J.C., McCarthy, G., 1995. Face-sensitive regions in human extrastriate cortex studied in functional MRI. J. Neurophysiol. 74, 1192–1199.

Tabert, M.H., Borod, J.C., Tang, C.Y., Lange, G., Wei, T.C., Johnson, R., Nusbaum, A.O., Buchsbaum, M.S., 2001. Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: an fMRI study. Neuropsychologia 39, 556–573.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Tranel, D., Damasio, A.R., 1985. Knowledge without awareness: an autonomic index of facial recognition by prosopagnosics. Science 228, 1453–1454.

Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J., 2001. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30, 829–841.

Vuilleumier, P., Armony, J.L., Driver, J., Dolan, R.J., 2003. Distinct spatial frequency sensitivities for processing faces an emotional expressions. Nat. Neurosci. 6, 624–631.

Whalen, P.J., Rauch, S.L., Etoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J. Neurosci. 18, 411–418.

Whalen, P.J., Shin, L.M., McInerney, S.C., Fischer, H., Wright, C.I., Rauch, S.L., 2001. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion 1, 70–83.

Winkielman, P., Zajonc, R.B., Schwartz, N., 1997. Subliminal affective priming resists attributional interventions. Cogn. Emot. 11, 433–465.

Write, 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.

Yamane, S., Kaji, S., Kawano, K., 1988. What facial features activate face neurons in the inferotemporal cortex of the monkey? Exp. Brain Res. 73, 209–214.

Zajonc, R.B., 1980. Feeling and thinking: preferences need no inferences. Am. Psychol. 35, 151–175.

Zald, D.H., 2003. The human amygdala and the emotional evaluation of sensory stimuli. Brain Res. Rev. 41, 88–123.