ACADEMIC PRESS

Available online at www.sciencedirect.com
SCIENCE DIRECT®

NeuroImage

NeuroImage 20 (2003) 1734–1742

www.elsevier.com/locate/ynimg

Neural substrates participating in acquisition of facial familiarity: an fMRI study

H. Kosaka,[a,b,*] M. Omori,[a] T. Iidaka,[c] T. Murata,[a] T. Shimoyama,[a] T. Okada,[d] N. Sadato,[d] Y. Yonekura,[b] and Y. Wada[a]

[a] *Department of Neuropsychiatry, Fukui Medical University, Matsuoka, Fukui, 910-1193, Japan*
[b] *Department of Biological Imaging Research Center, Fukui Medical University, Matsuoka, Fukui 910-1193, Japan*
[c] *Department of Human Information Processing, School of Informatics and Sciences, Nagoya University, Nagoya, Aichi, 464-8601, Japan*
[d] *Department of Cerebral Research, National Institute for Physiological Sciences, Okazaki, Aichi, 444-8585, Japan*

Received 17 April 2003; revised 29 June 2003; accepted 17 July 2003

Abstract

The amygdala is related to recognition of faces and emotions, and functional magnetic resonance imaging (fMRI) studies have reported that the amygdala is habituated over time with repetition of facial stimuli. When subjects are presented repeatedly with unfamiliar faces, they come to gradually recognize the unfamiliar faces as familiar. To investigate the brain areas participating in the acquisition of familiarity to repeatedly presented unfamiliar faces, we conducted an fMRI study in 16 healthy subjects. During the task periods, the subjects were instructed to see presented unfamiliar faces repeatedly and to judge whether the face was male or female or whether the face had emotional valences. The experiment consisted of nine sessions. To clarify the brain areas that showed increasing or decreasing activation as the experimental session proceeded, we analyzed the fMRI data using specified linear covariates in the face recognition task from the first session to the ninth session. Imaging data were investigated on a voxel-by-voxel basis for single-group analysis according to the random effect model using Statistical Parametric Mapping. The bilateral posterior cingulate cortices showed significant increases in activity as the experimental sessions proceeded, while the activation in the right amygdala and the left medial fusiform gyrus decreased. Thus, the posterior cingulate cortex may play an important role in the acquisition of facial familiarity.

Keywords: FMRI; Familiarity; Posterior cingulate cortex; Amygdala; Habituation; Face

Introduction

Face perception is the most developed visual perceptual skill in humans and plays a critical role in social interactions (Haxby et al., 2002). Novel, unknown faces, when seen for the first time, can potentially represent a threat or a danger and lead to a rapid shift of attention in the human brain. However, repeated presentation of those novel stimuli will make such cognitive responses wane and gradually yield instead a feeling of already-seen, i.e., familiar faces (Dubois et al., 1999; Wright et al., 2001). Disturbance of the neural system related to such habituation and/or familiarity acquisition to repeatedly presented unknown faces may cause the disordered social cognition sometimes seen in psychiatric disorders, in which the patients express exaggerated anxiety responses to other people, misjudge the approachability and trustworthiness of those around them, or mistake even familiar people for an assailants.

The amygdala plays a crucial role in the recognition of faces and emotions (LeDoux, 2000; Davis and Whalen, 2001). A functional magnetic resonance imaging (fMRI) study reported that the right amygdala exhibits a greater response to novel faces than to familiar faces, all with an emotionally neutral expression (Schwartz et al., 2003). It has also been revealed that amygdala activation is habitu-

* Corresponding author. Department of Neuropsychiatry, Fukui Medical University, Matsuoka, Fukui, 910-1193, Japan. Fax: +81-776-61-8136.

E-mail address: hirotaka@fmsrsa.fukui-med.ac.jp (H. Kosaka).

1053-8119/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S1053-8119(03)00447-6

ated with repeated facial stimuli (Breiter et al., 1996; Wright et al., 2001; Thomas et al., 2001).

On the other hand, a candidate area participating in the acquisition of facial familiarity is the posterior cingulate cortex. It has been reported that the posterior cingulate cortex is activated commonly in familiar (previously learned) word recognition minus reading word condition and familiar face recognition minus gender classification conditions in an $H_2{}^{15}O$ positron emission tomography (PET) study (Kim et al., 1999). FMRI studies showed greater posterior cingulate activation during explicit recognition of famous faces (well-known entertainers, politicians, and sports figures) than during that of unfamiliar faces (Leveroni et al., 2000) and activity also increased under experimental conditions with personally known faces and voices (friends and relatives of the subjects) relative to the conditions with unfamiliar ones (Shah et al., 2001). These studies proposed that the posterior cingulate cortex is a key area involved in assessing the familiarity of a person.

To our knowledge, however, no prior study has investigated the time course of activation in particular brain areas, in which the familiarity was gradually acquired over time with repeated exposure to unknown faces. The purpose and the new aspects of the present study were to demonstrate using fMRI that the activation in the posterior cingulate cortex increases as unfamiliar facial stimuli are presented repeatedly. It was predicted that the amygdala would show greater initial response and then habituate to the unfamiliar faces, while posterior cingulate activity would increase reciprocally as familiarity was acquired.

Materials and methods

Subjects

Sixteen healthy subjects, 8 males and 8 females, participated in the present study. Their ages ranged from 22 to 28 years, with a mean age of 24.5 years (standard deviation (SD), 1.7 years). The subjects had no history of neurological or psychiatric disease or drug or alcohol abuse. All subjects were strongly right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The protocol was approved by the Ethical Committee of Fukui Medical University, and all subjects gave written informed consent for the study. None were taking any medication at the time of the study.

Materials and procedure

If a small number of individual facial stimuli are simply repeated, amygdala activity rapidly habituates (Bordi and LeDoux, 1992). To make subjects habituate to unfamiliar faces rather more slowly may allow for better detection of the brain areas that show increasing activity over time with repeated facial stimuli. We thus devised experimental tasks as follows. A relatively large number of individual faces were used as experimental stimuli with a relatively large number of repetitions. Then, two kinds of task with these facial stimuli depicting three different emotion types (i.e., positive, negative, and neutral) were used, and subjects were instructed to judge the gender or the emotional valences of the faces. Since it was difficult for the subjects to habituate to the tasks per se and to notice the repeated presentation of the same facial stimuli, the acquisition of familiarity with the faces would be incidental for them, that is, it was not integral to the task.

Digitized gray scale pictures of 20 unfamiliar faces (10 males and 10 females) with positive (happy), negative (angry, disgusted, or sad), or neutral emotion, were used as materials. To establish the validity and reliability of the facial stimuli used, a sample of 10 healthy controls was asked to rate each face according to emotion type and intensity, as described previously (Kosaka et al., 2002).

The experiment consisted of nine sessions (Fig. 1). Each session was composed of eight blocks, four control and four face recognition task blocks. Each block was 21 s long, alternating control and task. A list of 10 faces was assigned to each block, and the faces were presented at a rate of 1.8 s with a 0.3-s intertrial interval. As described previously, we used two kinds of task conditions, i.e., gender-discrimination (five sessions: three neutral face sessions, one positive face session, and one negative face session) and emotion-judgment (four sessions: two neutral face sessions, one positive face session, and one negative face session). Before each experimental session, the subjects were instructed to judge whether the face was male or female during the gender-discrimination task or whether the face had emotional valences or not during the emotion-judgment task and to respond by pressing one of two buttons of the response box with their right index and middle fingers. During the neutral face sessions, all 10 faces per block had neutral emotion. During the emotional face sessions, 8 faces had emotionally positive expression for the positive face sessions or negative expression for the negative face sessions, and 2 faces had neutral emotion per block. The order of the nine sessions was counterbalanced across subjects. Twenty actors' faces were used as the experimental stimuli; each actor's face was presented 2 times per session and presented 18 times across all sessions. Under the control condition, the subjects were instructed to discriminate whether the object was a circle or a square (figure-discrimination). These stimuli were presented at the same rate and in the same format as the stimuli under the task condition. Before the experiment, a shorter version of the experimental task was administered to confirm that the subjects could perform at an average level.

During scanning, the stimuli were projected onto a half transparent screen using a LCD projector connected to a personal computer by which the stimuli were generated. The subjects saw the stimuli through a tilted mirror attached to the head coil of the scanner.

Image acquisition and analysis

Functional images of the whole brain were acquired using T2*-weighted, gradient echo, EPI sequences with a 3-T MR imager (Signa Horizon; General Electric Medical Systems, Milwaukee, WI, USA) and a standard birdcage head coil. Each volume consisted of 34 axial slices, with a slice thickness of 2.7 mm, with a 0.3-mm gap. The time interval between two successive acquisitions of the same image was 3000 ms, the echo time was 30 ms, and the flip angle was 90°. The digital in-plane resolution was 64 × 64 pixels, with a pixel dimension of 2.97 × 2.97 mm. The anatomical image was also acquired (2D FSE: TR, 6 s; TE, 66 ms; flip angle, 90°; 256 × 256 matrix; and 112 axial slices 1.5 mm thick). Tight but comfortable foam padding was placed around the subject's head to minimize head motion. After discarding the first 4 images per session due to the unsteady longitudinal magnetization, 504 successive EPI images (7 images per block, 56 images per session) were subjected to analysis. Image processing and statistical analysis was performed using Statistical Parametric Mapping (SPM99: the Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1995) implemented in Matlab 5.3 (The Mathworks, Inc., USA). First, to correct for dislocations caused by head motion, all EPI images were realigned. These images were then normalized to the Montreal Neurological Institute (MNI) atlas (Evans et al., 1994) using the parameter obtained from the normalization process of the anatomical image that was coregistered to the first EPI image beforehand. Finally, the images were smoothed using an 8-mm Gaussian kernel.

Data-analysis

First, analysis was performed on an individual basis. The mean signal intensity of the imaged brain areas was proportionally scaled to 100 arbitrary units for each functional image volume in order to remove the effect of global signal change. The expected signal changes caused by the tasks were modeled with a boxcar function convolved with a hemodynamic response function and regression analysis was performed for each and every voxel. Signal drifts below 1/84 Hz were also modeled and excluded from the analysis to avoid artifacts. The analysis made contrast images that held percentage of signal change values at each voxel for the face recognition tasks compared with the control condition. To make inferences at a single-group level (Friston et al., 1999), these images were analyzed with one-sample *t* tests on a voxel-by-voxel basis.

First, we clarified the main effect of overall face recognition tasks in the nine sessions. The resulting areas of activation were characterized in terms of their peak. The statistical threshold was set at $P < 0.05$ (corrected) for each voxel. Second, a subtraction between the images for face conditions during the gender-discrimination tasks and the images for face conditions during the emotion-judgment tasks was conducted. A subtraction among the images for neutral face conditions, the images for positive face conditions, and the images for negative face conditions was also conducted. The statistical threshold was set at $P < 0.05$ (corrected) for each voxel. Third, to clarify the brain areas that showed increasing or decreasing activation as the experimental session proceeded, we analyzed the fMRI data using specified linear covariates (−4, −3, −2, −1, 0, 1, 2, 3, 4) in the face recognition task from the first session to the ninth session. Unless otherwise specified, the statistical threshold was set at $P < 0.05$ (corrected) for height in the analysis of increasing or decreasing activity over time for each voxel. Activated clusters were superimposed on the T1-weighted template images. These data were averaged across the subjects, and the magnitude of increase from the control condition was plotted as a function of time (nine sessions).

Results

Behavioral results

Under the control conditions (figure-discrimination task), the mean (± SD) percentage of correct responses was 99.3 ± 1.1%, and the mean reaction time was 451.3 ± 76.6 msec. In the facial task conditions (i.e., gender-discrimination, and emotion-judgment), the mean percentages of correct responses were 93.9 ± 4.7 and 93.1 ± 3.6%, and the mean reaction times were 671.8 ± 84.9 and 811.3 ± 107.0 ms, respectively. There were no significant differences in percentages of correct responses ($t = 0.712$, $df = 15$, $P = 0.4877$) between gender-discrimination and emotion-judgment tasks, while significant differences were found in reaction time ($t = -6.317$, $df = 15$, $P < 0.0001$). The mean percentages of correct responses were 93.6 ± 4.4 and 93.6 ± 3.4%, and the mean reaction times were 740.0 ± 91.0 and 726.1 ± 94.6 ms, in the first half of sessions (from first to fifth) and the latter half of sessions (from sixth to ninth), respectively. There were no significant differences in percentages of correct responses ($t = 0.007$, $df = 15$, $P = 0.9947$) and reaction time ($t = 0.730$, $df = 15$, $P = 0.4766$) between the first half of sessions and the latter half of sessions. After their experiments, most subjects stated that they became aware of the faces of the same actors presenting repeatedly in the latter sessions.

Imaging results

In the group analysis, areas of significant activation during the overall face recognition tasks were the bilateral inferior frontal gyri [Brodmann areas (BA) 45, 47], middle frontal gyri (BA 9), superior parietal lobuli (BA 7), inferior occipital gyri (BA 18, 19), lateral fusiform gyri (BA 37), supplementary motor area (BA 6), and right entorhinal cortex (BA 28) ($P < 0.05$, corrected; Table 1; Fig. 2). The

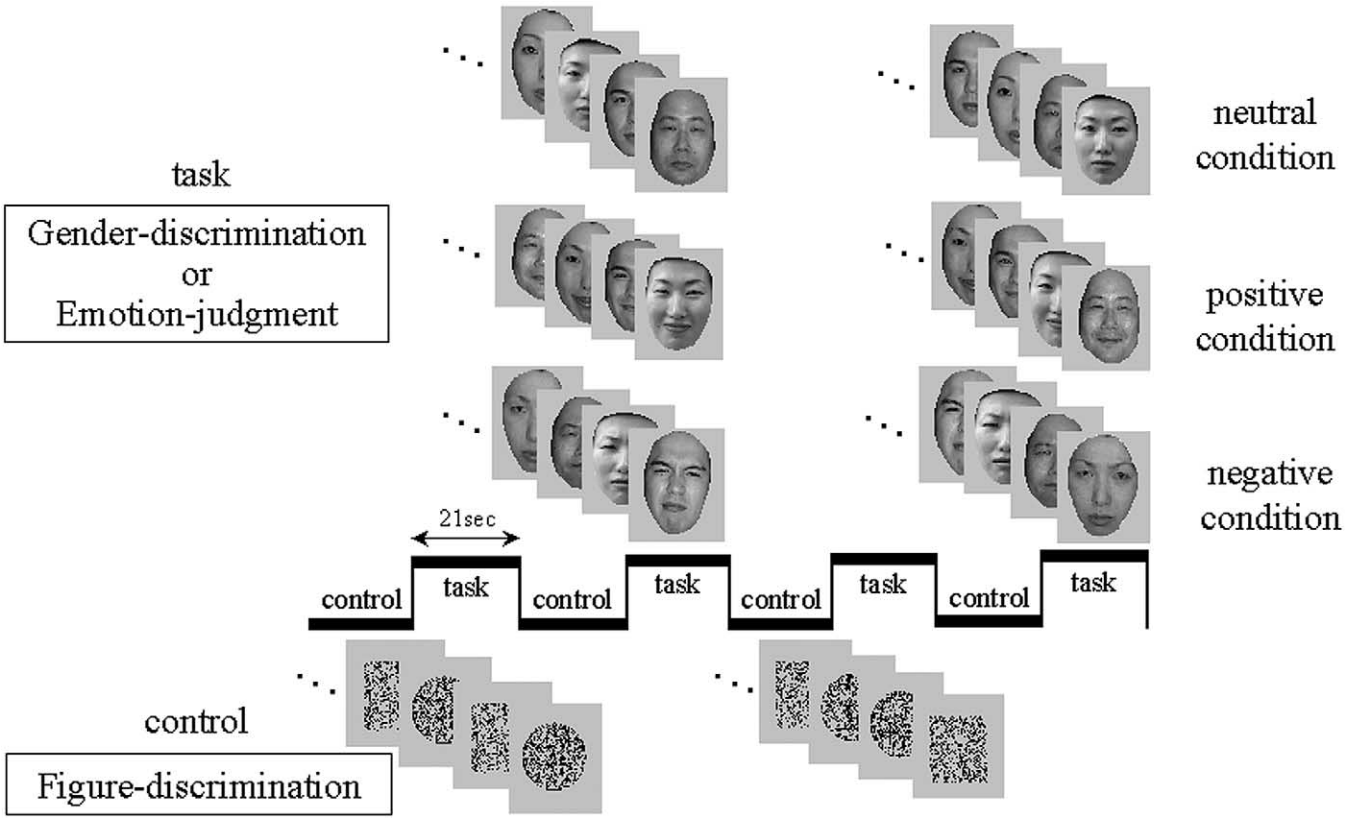


Fig. 1. The experimental task design. The experiment consisted of nine sessions. Each session was composed of eight blocks; four control and four face recognition task (neutral, positive, or negative face condition for neutral face, positive face, or negative face session, respectively) blocks. Each block was 21 s long, alternating control and task. Under the control condition, the subjects were instructed to discriminate whether the object was a circle or a square (figure-discrimination). Under the task condition, the subjects were instructed to judge whether the face was male or female during the gender-discrimination task or whether the face had emotional valences during the emotion-judgment task. The order of nine face recognition sessions was counterbalanced across subjects.

neural activity during the emotion-judgment task was higher than that during the gender-discrimination task in the bilateral middle and inferior frontal gyri (BA 9, 45, 46, 47), supplementary motor area (BA 6), right parietal cortex (BA 40), and middle temporal gyrus (BA 22) (corrected, $P < 0.05$). However, there was no significant difference in activation among neutral, positive, and negative face conditions (corrected, $P < 0.05$).

Table 1
The areas activated during all facial recognition tasks

Area	BA	Coordinates			Z value
		x	y	z	
L inferior frontal gyrus	45/47	−30	32	−2	5.02
R inferior frontal gyrus	45/47	40	28	−2	4.93
L middle frontal gyrus	9	−48	22	36	5.59
R middle frontal gyrus	9	50	18	36	5.95
L superior parietal lobe	7	−30	−66	44	4.29
R superior parietal lobe	7	26	−66	40	5.48
L inferior occipital gyrus	18/19	−34	−80	−14	5.89
R inferior occipital gyrus	18/19	40	−84	0	6.32
L lateral fusiform gyrus	37	−36	−52	−20	4.77
R lateral fusiform gyrus	37	38	−62	−18	3.80
Supplementary motor area	6	2	16	60	4.94
R entorhinal cortex	28	18	−28	−6	4.91

Note. L, left; R, right; BA, Brodmann area; *x*, *y*, *z*, stereotaxic coordinates as given in the Talairach and Tournoux atlas. The statistical threshold was set to $P < 0.05$ (corrected).

Table 2 presents the brain areas that showed increasing or decreasing activation as the experimental sessions proceeded, which were analyzed using specified linear covariates. The neural activities in the bilateral posterior cingulate cortices [BA 23, 31; (−2, −32, 22) and (6, −32, 22) at Talairach coordinates (Talairach and Tournoux, 1988)] significantly increased over time (corrected, $P < 0.05$; Fig. 3). On the other hand, there were no significant voxels that showed the decreasing activity over time thresholded at $P < 0.05$ (corrected). Since the hypothesis existed for the habituation effects on the amygdaloid activity which have been reported previously (Breiter et al., 1996; Wright et al., 2001; Thomas et al., 2001), the statistical threshold was reset for the analysis of decreasing activity at $P < 0.001$ (uncorrected) for height and clusters larger than 10 contiguous voxels. The activity in the bilateral amygdalae [(−18, −14, −16) and (22, −10, −18)] and the left medial fusiform gyrus [BA

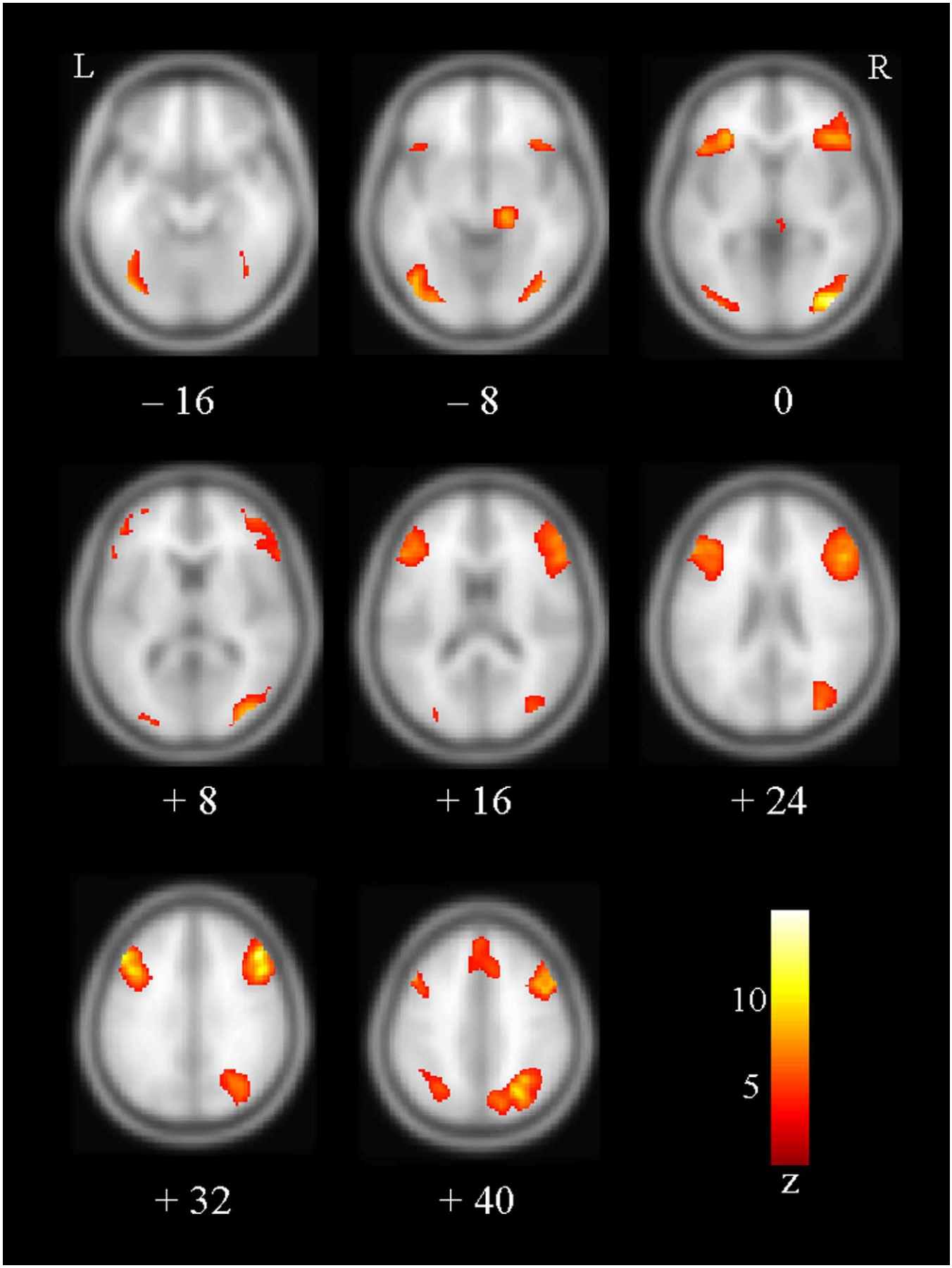
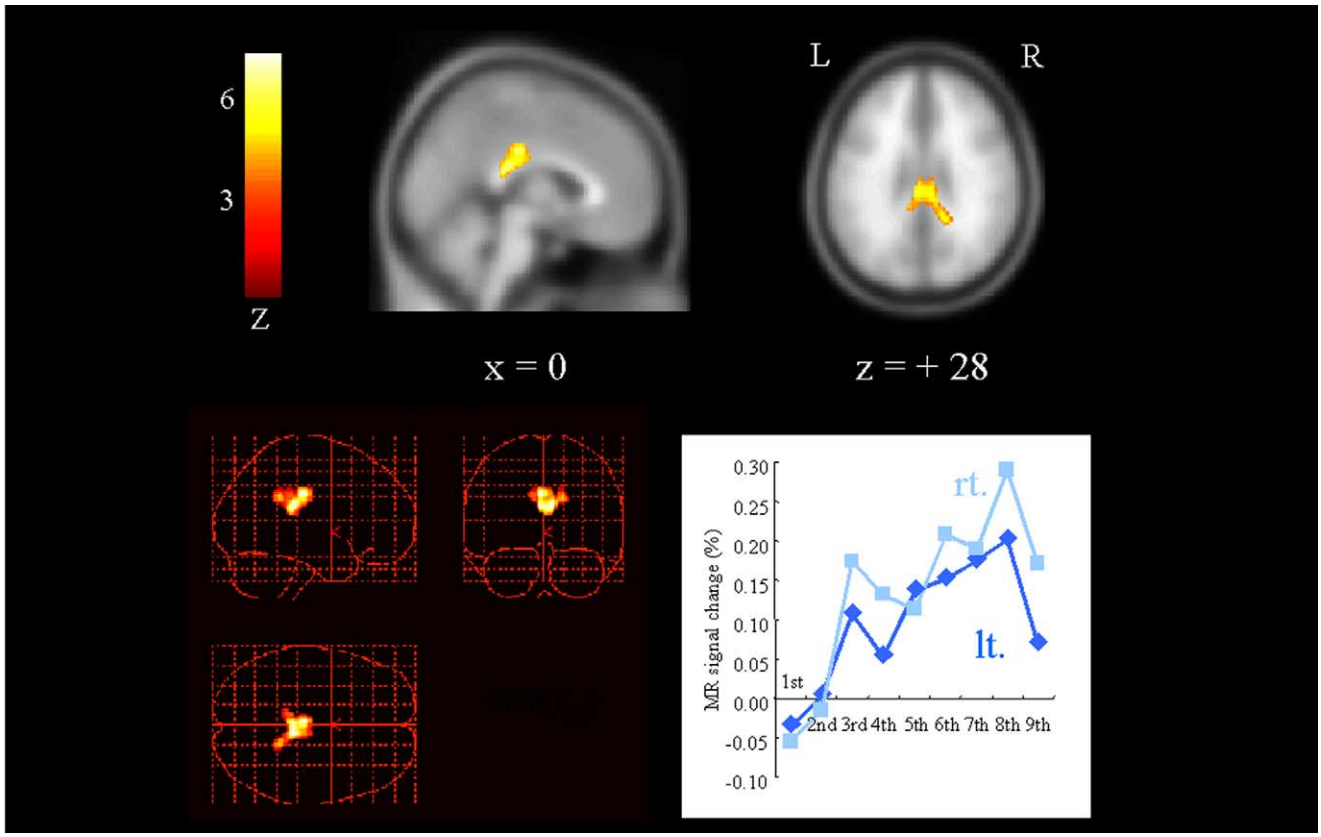
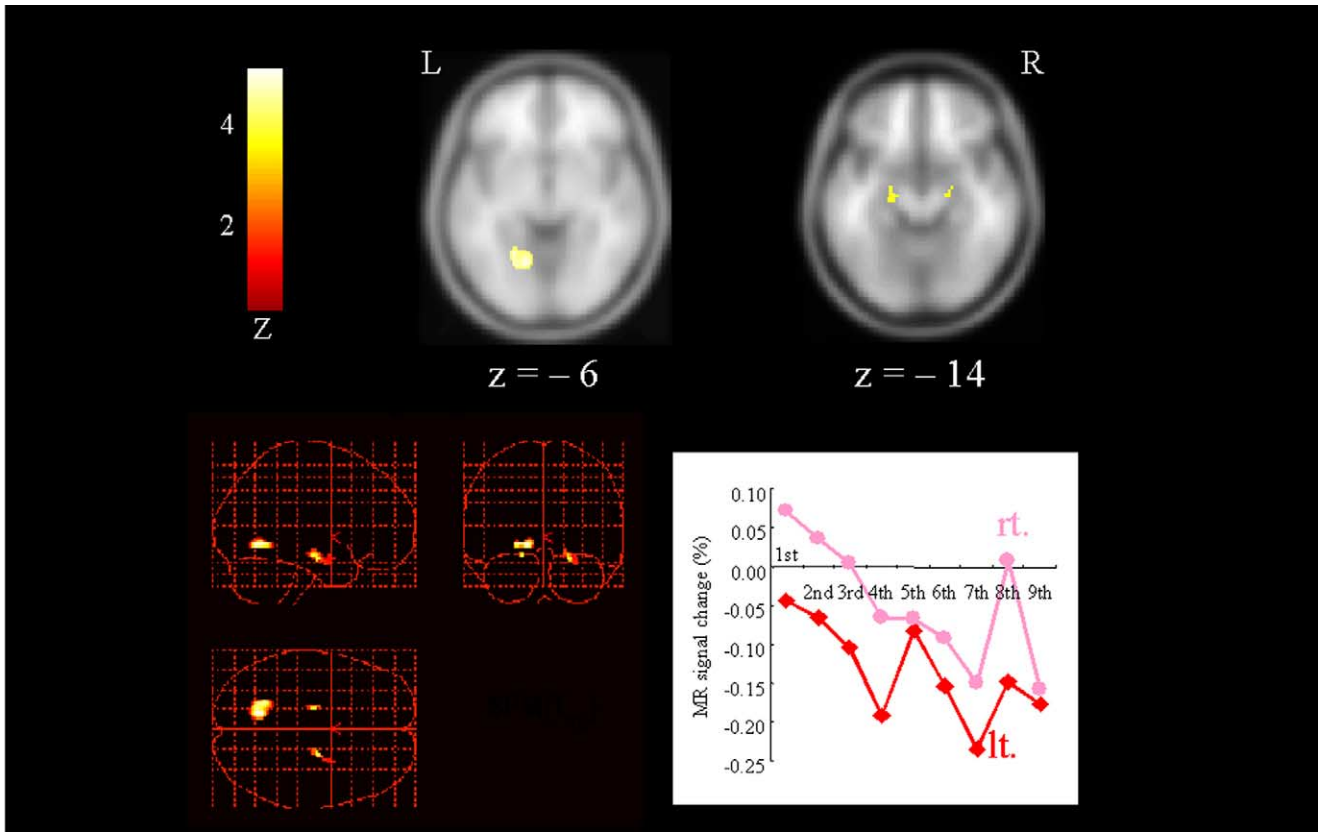


Fig. 2. Horizontal slices of the main effect of overall face recognition tasks in the nine sessions. The statistical threshold was $P < 0.05$, corrected for multiple comparisons at the cluster level. The *Z* score is as indicated by the color bar, the statistical significance increasing as red proceeds to white. Images are shown in the Talairach space (Talairach and Tournoux, 1988) with the *z* coordinate label. The left side of the brain corresponds to the left side of the image and the frontal region to the top.


6
3
Z
L
R
x = 0
z = + 28
MR signal change (%)
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
1st
2nd 3rd 4th 5th 6th 7th 8th 9th
rt.
lt.

3


4
2
Z
L
R
z = – 6
z = – 14
MR signal change (%)
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
1st
2nd 3rd 4th 5th 6th 7th 8th 9th
rt.
lt.

4

Table 2
The areas showing decreasing or increasing activation as the experimental sessions proceeded

Area	BA	Coordinates			*Z* value
		x	*y*	*z*	
Increasing activity					
L posterior cingulate cortex	23/31	−2	−32	22	4.60
R posterior cingulate cortex	23/31	6	−32	22	4.65
Decreasing activity					
L amygdala		−18	−14	−16	3.50
R amygdala		22	−10	−18	3.53
L medial fusiform gyrus	19/37	−14	−60	−6	3.71

Note. L, left; R, right; BA, Brodmann area; *x, y, z,* stereotaxic coordinates as given in the Talairach and Tournoux atlas. The statistical threshold was set to $P < 0.05$ (corrected) for the analysis of increasing activity and to $P < 0.001$ (uncorrected) for decreasing activity.

19, 37; (−14, −60, −6)] was significantly decreased as the sessions proceeded at the lenient threshold, although the left amygdala never demonstrated a greater activation relative to the control conditions through all sessions (Fig. 4). In the individual analysis, the neural activities in these cortical regions had a tendency to show similar patterns of activation.

Discussion

We observed that the response of the posterior cingulate cortex increased and that of the amygdala decreased as the experimental sessions proceeded in the present study.

The present time course of decreased changes in the right amygdala activation is supported by other studies, which showed habituated amygdala responses to the emotionally valenced faces (Breiter et al., 1996; Wright et al., 2001) or familiar "ingroup" faces (Hart et al., 2000). These studies reported less amygdala activation during the second (late) scan than during the first (early) scan. There was a possibility that the subjects became habituated to unfamiliar facial stimuli or perceived unfamiliar faces as familiar ones gradually with repeated stimulus exposures, even if the familiarity acquisition was not integral but incidental to the task. In fact, most of our subjects stated after the experiments that they became aware of same actors' faces presenting repeatedly in the latter half of sessions. Since we incorporated two different tasks, i.e., gender-discrimination and emotion-judgment, together into the experiment and there were no significant differences in percentages of correct response and reaction time between the first half of sessions and the latter half of sessions, it is unlikely that the reduced amygdala signal in the present study was due to a habituation effect to the experimental task per se. Moreover, the order of emotional face sessions and neutral face sessions was counterbalanced across subjects, and neutral face conditions were more frequent than positive face or negative face conditions. There was no significant difference in activation among the neutral, positive, and negative face conditions. Taken together, it is also unlikely that the amygdala signal reduction was due to a habituation effect to emotion. Thus, it is suggested that the right amygdala response shown in the present study reflects habituation to repeated presentation of unfamiliar facial stimuli per se.

Our results showed that the bilateral lateral fusiform gyri were significant activation areas during all face recognition tasks compared with the control conditions. The signal change in the medial portion of the left fusiform gyrus was significantly decreased over time at the lenient threshold, although this activation was not significant during the face recognition relative to the control conditions. While face recognition activates more inferior and lateral aspects of the fusiform gyrus, object recognition such as the present control condition activates more medial aspects of the fusiform gyrus (Chao et al., 1999; Ishai et al., 2000; Joseph, 2001). The decreased MR signal in the left medial fusiform gyrus may reflect that activation in this portion was relatively persistent during the figure discrimination under the control conditions instead of decreasing participation in face recognition as the task block proceeded.

As for the posterior cingulate cortex, greater activation was reported during explicit recognition of famous faces compared to during that of recently encoded faces or unfamiliar faces seen for the first time (Leveroni et al., 2000) or during implicit recognition of familiar (friends') faces and voices relative to during that of unfamiliar faces and voices (Shah et al., 2001) in fMRI studies. Kim et al. (1999) also reported that explicit recognition of familiar (previously

Fig. 3. The brain areas and signal change showing increasing activation as the nine experimental sessions proceeded. (Top row) The bilateral posterior cingulate cortices increasing activity superimposed on the MNI normalization T1-weighted template in sagittal and transverse images. The statistical threshold was $P < 0.05$, corrected for multiple comparisons at the cluster level. The left side of the brain corresponds to the left side of the image and the frontal region to the top. The *Z* score is as indicated by the color bar, the statistical significance increasing as red proceeds-to white. (Bottom left) Statistical parametric maps are shown in standard anatomical space. The three-dimensional information was collapsed into two-dimensional sagittal, coronal, and transverse images (i.e., maximum intensity projections viewed from the right, back, and top of the brain). (Bottom right) MR signal change in the bilateral posterior cingulate cortices over time. The light blue line represents the signal change in the right posterior cingulate cortex, and the deep blue line represents the left posterior cingulate cortex.

Fig. 4. The brain areas and signal change showing decreasing activation as the nine experimental sessions proceeded. (Top row) The bilateral amygdalae and the left medial fusiform gyrus decreasing activity superimposed on the MNI normalization T1-weighted template in transverse images. The statistical threshold was $P < 0.001$, uncorrected for multiple comparisons at the voxel level and clusters larger than 10 contiguous voxels. Other details are the same as described in the legends of Fig. 3. (Bottom right) MR signal change in the bilateral amygdalae over time. The pink line represents the signal change of the right amygdala, and the red line represents the left amygdala.

learned) faces and words was associated with increased neural activity in the posterior cingulate cortex relative to that of novel faces and words using PET. These studies suggested that the posterior cingulate cortex participates in assessing the familiarity of a person. Further, Henson et al. (2002) demonstrated that implicit processing of two repeated presentations of familiar or unfamiliar facial stimuli, in which subjects judged whether a face was famous or nonfamous during fMRI, produced increased responses from the first to second presentation (the "repetition enhancement" effect) in several regions, including the bilateral posterior cingulate cortices. However, they had not described differences in the repetition effects between familiar and unfamiliar facial stimuli in this region. In the present study, the MR signal in the bilateral posterior cingulate cortices elevated little by little over time with the repetition of facial stimuli. In consideration of the references described above, the increasing activity in the posterior cingulate cortex may reflect the neural process, in which the subjects perceive unfamiliar faces as familiar with repeated presentation. These findings suggest that the posterior cingulate cortex plays an important role in the acquisition of facial familiarity.

Other roles of the posterior cingulate cortex have been also reported. Severe metabolism reduction in the posterior cingulate cortex in patients with Alzheimer's disease and diffuse Lewy body disease was reported using PET, and it has been suggested that this hypofunction is related to learning and memory impairment in early stages of Alzheimer's disease (Minoshima et al., 1994, 1997, 2001; Reiman et al., 1996). Activation of this region has been described during verbal memory (Grasby et al., 1993) and during the encoding of episodic memory (Fletcher et al., 1995). It is suggested that the posterior cingulate cortex is involved in the retrieval of autobiographical memories elicited by familiar name-cued recall (Maddock et al., 2001). The increased activation of the posterior cingulate cortex in the present study may thus be related not only to the acquisition of facial familiarity, but also to implicit monitoring of retrieved facial memories.

While the response of the right amygdala decreased as the sessions proceeded, the bilateral posterior cingulate activation increased in the present study. There are few reports on a direct neural network between the posterior cingulate cortex and amygdala. However, the posterior cingulate cortex has anatomical connections with the hippocampal formation and close functional association with the medial temporal memory systems (Olson and Musil, 1992; Kobayashi and Amaral, 2000). The hippocampal formation also has strong reciprocal connections with the amygdala. Moreover, while the posterior cingulate cortex is reciprocally connected to regions involved in emotional processing, including the anterior cingulate cortex (Baleydier and Mauguiere, 1980; Vogt et al., 1992), the anterior cingulate also has reciprocal connections with the amygdala (Musil and Olson, 1988; Sesack et al., 1989; Zeng and Stuesse, 1991). Thus, the posterior cingulate cortex and amygdala may work reciprocally, via other brain regions such as the hippocampus or the anterior cingulate cortex, in the habituation and acquisition of familiarity to unfamiliar facial stimuli presented repeatedly, as in our experiment.

The left amygdala revealed no activation compared to the control-conditions through the present nine sessions. We have previously reported that the right amygdala is generally involved in face processing per se, whereas the left amygdala is specifically associated with information with a negative valence (Iidaka et al., 2001). Schwartz et al. (2003) showed that novel facial stimuli with neutral expressions activated only the right amygdala more than familiar faces. The reason for the lack of left amygdala activation in the present study may be that facial stimuli with an emotionally neutral expression and with a positive emotion were used in five and two of the nine sessions, respectively, while there were only two sessions using faces with negative emotion. Further, the left amygdala appeared to show a significant increasing negative response to the facial stimuli relative to the control conditions over the nine sessions. If the amygdala and posterior cingulate cortex work reciprocally in the repetitive presentation of the unfamiliar facial stimuli, it may be speculated that the former activity even including the left side was suppressed relatively as the latter activity increased.

The amygdala plays a central role in processing the social relevance of information gleaned from faces (Haxby et al., 2000, 2002). Its greater activation to unknown than known faces has suggested that unknown faces could be detected as a potential threat (Dubois et al., 1999; Schwartz et al., 2003). We have reported that patients with schizophrenia show greater amygdala activation during emotional face judgment tasks than healthy controls and speculated that the exaggerated amygdala activation may reflect impaired gating of sensory input containing emotion in schizophrenia (Kosaka et al., 2002). It is possible that patients with schizophrenia show no or less habituation of amygdala responses to unfamiliar facial stimuli used in our previous study than to rapid habituation in the control subjects. Such an impairment of amygdala habituation may cause schizophrenics to mistake even familiar people as untrustworthy, dangerous, or potential assailants. In consideration of the present results, less increasing posterior cingulate response to repetitive unfamiliar facial stimuli may also be a putative maker in patients with schizophrenia who exhibit such cognitive impairments in social interaction.

Acknowledgment

This study was supported by Grant-in-Aid for Scientific Research 14207039 from the JSPS.

References

Baleydier, C., Mauguiere, F., 1980. The duality of the cingulate gyrus in monkey: neuroanatomical study and functional hypothesis. Brain 103, 525–554.

Bordi, F., LeDoux, J., 1992. Sensory tuning beyond the sensory system: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. J. Neurosci. 12, 2493–2503.

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.

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

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Mol. Psychiatr. 6, 13–34.

Dubois, S., Rossion, B., Schiltz, C., Bodart, J.M., Michel, C., Bruyer, R., Crommelinck, M., 1999. Effect of familiarity on the processing of human faces. NeuroImage 9, 278–289 doi:10.1006/nimg.1998.0409.

Evans, A.C., Kamber, M., Collins, D.L., Macdonald, D., 1994. An MRI-based probablistic atlas of neuroanatomy. in: Shorvon, S., Fish, D., Andermann, F., Bydder, G.M., Stefan, H. (Eds.), Magnetic resonance scanning and epilepsy, NATO ASI series A Life Sciences, Vol. 264. Plenum, New York, pp. 263–274.

Fletcher, P.C., Frith, C.D., Grasby, P.M., Shallice, T., Frackowiak, R.S., Dolan, R.J., 1995. Brain systems for encoding and retrieval of auditory-verbal memory: an in vivo study in humans. Brain 118, 401–416.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parameter maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Friston, K.J., Holmes, A.P., Worsley, K.J., 1999. How many subjects constitute a study? NeuroImage 10, 1–5 doi:10.1006/nimg.1999.0439.

Grasby, P.M., Frith, C.D., Friston, K.J., Bench, C., Frackowiak, R.S., Dolan, R.J., 1993. Functional mapping of brain areas implicated in auditory–verbal memory function. Brain 116, 1–20.

Hart, A.J., Whalen, P.J., Shin, L.M., McInerney, S.C., Fischer, H., Rauch, S.L., 2000. Differential response in the human amygdala to racial outgroup vs ingroup face stimuli. Neuroreport 11, 2351–2355.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends Cogn. Sci. 4, 223–233.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2002. Human neural systems for face recognition and social communication. Biol. Psychiatry 51, 59–67.

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.

Iidaka, T., Omori, M., Murata, T., Kosaka, H., Yonekura, Y., Okada, T., Sadato, N., 2001. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. Cogn. Neurosci. 15, 1035–1047.

Ishai, A., Ungerleider, L.G., Haxby, J.V., 2000. Distributed neural systems for the generation of visual images. Neuron 28, 979–990.

Joseph, J.E., 2001. Functional neuroimaging studies of category specificity in object recognition: a critical review and meta-analysis. Cogn. Affect. Behav. Neurosci. 2, 119–136.

Kim, J.J., Andreasen, N.C., O'Leary, D.S., Wiser, A.K., Ponto, L.L., Watkins, G.L., Hichwa, R.D., 1999. Direct comparison of the neural substrates of recognition memory for words and faces. Brain 122, 1069–1083.

Kobayashi, Y., Amaral, D.G., 2000. Macaque monkey retrosplenial cortex: I. Three-dimensional and cytoarchitectonic organization. J. Comp. Neurol. 426, 339–365.

Kosaka, H., Omori, M., Murata, T., Iidaka, T., Yamada, H., Okada, T., Takahashi, T., Sadato, N., Itoh, H., Yonekura, Y., Wada, Y., 2002. Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. Schizophr. Res. 57, 87–95.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184.

Leveroni, C.L., Seidenberg, M., Mayer, A.R., Mead, L.A., Binder, J.R., Rao, S.M., 2000. Neural systems underlying the recognition of familiar and newly learned faces. J. Neurosci. 20, 878–886.

Maddock, R.J., Garrett, A.S., Buonocore, M.H., 2001. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 104, 667–676.

Minoshima, S., Foster, N.L., Kuhl, D.E., 1994. Posterior cingulate cortex in Alzheimer's disease. Lancet 344, 895.

Minoshima, S., Giordani, B., Berent, S., Frey, K.A., Foster, N.L., Kuhl, D.E., 1997. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann. Neurol. 42, 85–94.

Minoshima, S., Foster, N.L., Sima, A.A., Frey, K.A., Albin, R.L., Kuhl, D.E., 2001. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann. Neurol. 50, 358–365.

Musil, S.Y., Olson, C.R., 1988. Organization of cortical and subcortical projections to anterior cingulate cortex in the cat. J. Comp. Neurol. 272, 203–218.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9, 97–113.

Olson, C.R., Musil, S.Y., 1992. Topographic organization of cortical and subcortical projections to posterior cingulate cortex in the cat: evidence for somatic, ocular, and complex subregions. J. Comp. Neurol. 324, 237–260.

Reiman, E.M., Caselli, R.J., Yun, L.S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S.N., Osborne, D., 1996. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein. E. N. Engl. J. Med. 334, 752–758.

Schwartz, C.E., Wright, C.I., Shin, L.M., Kagan, J., Whalen, P.J., McMullin, K.G., Rauch, S.L., 2003. Differential amygdalar response to novel versus newly familiar neutral faces: a functional MRI probe developed for studying inhibited temperament. Biol. Psychiatry 53, 854–862.

Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J. Comp. Neurol. 290, 213–242.

Shah, N.J., Marshall, J.C., Zafiris, O., Schwab, A., Zilles, K., Markowitsch, H.J., Fink, G.R., 2001. The neural correlates of person familiarity: a functional magnetic resonance imaging study with clinical implications. Brain 124, 804–815.

Thomas, K.M., Drevets, W.C., Whalen, P.J., Eccard, C.H., Dahl, R.E., Ryan, N.D., Casey, B.J., 2001. Amygdala response to facial expressions in children and adults. Biol. Psychiatry 49, 309–316.

Vogt, B.A., Finch, D.M., Olson, C.R., 1992. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb. Cortex 2, 435–443.

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.

Zeng, D., Stuesse, S.L., 1991. Morphological heterogeneity within the cingulate cortex in rat: a horseradish peroxidase transport study. Brain Res. 565, 290–300.