

Neuroimaging Study of the Human Amygdala -Toward an Understanding of Emotional and Stress Responses-

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The amygdala plays a critical role in the neural system involved in emotional responses and conditioned fear. The dysfunction of this system is thought to be a cause of several neuropsychiatric disorders. A neuroimaging study provides a unique opportunity for noninvasive investigation of the human amygdala. We studied the activity of this structure in normal subjects and patients with schizophrenia by using the face recognition task. Our results showed that the amygdala was activated by presentation of face stimuli, and negative face activated the amygdala to a greater extent than a neutral face. Under the happy face condition, the activation of the amygdala was higher in the schizophrenic patients than in control subjects. A single nucleotide polymorphism in the regulatory region of the serotonin type 3 receptor gene had modulatory effects on the amygdaloid activity. The emotion regulation had a significant impact on neural interaction between the amygdala and prefrontal cortices. Thus, studies on the human amygdala would greatly contribute to the elucidation of the neural system that determines emotional and stress responses. To clarify the relevance of the neural dysfunction and neuropsychiatric disorders, further studies using physiological, genetic, and hormonal approaches are essential.

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1. Introduction

The amygdala plays a critical role in the neural system that is involved in emotional responses and conditioned fear. The dysfunction of this system is thought to be a cause of several neuropsychiatric disorders (e.g., schizophrenia, depression, and anxiety disorder). A neuroimaging study using functional magnetic resonance imaging (fMRI) provides a unique opportunity for noninvasive investigation of the human amygdala with a high spatial resolution. We studied the activity of this structure in normal young subjects and patients with schizophrenia by using the face recognition task. Although the involvement of the amygdala in the processing of facial expressions has been investigated in human lesion studies, the mechanisms underlying neural response to facial stimuli are not yet completely understood. In the first study, we investigated this mechanism in normal young subjects. In the second study, we evaluated the effect of an implicit presentation of facial pictures on amygdala activation in normal subjects. Since impairments in the recognition of emotional expressions have been reported in schizophrenia, in the third study, we compared brain activation during facial recognition between patients with schizophrenia and normal controls. The serotonin (5-HT) system within the brain has been linked to various behaviors such as mood and anxiety, and to the biology of neuropsychiatric disorders. Therefore, in the fourth study, we compared the activity in the amygdala

between the different genotypes of the serotonin type 3 receptor polymorphism. Finally, we examined the interaction between the amygdala and prefrontal activity during emotion regulation by using a positron emission tomography.

2. Facial Expression and Amygdala

We investigated, using fMRI and healthy volunteers, how the amygdalae are activated while subjects are watching the faces with negative, positive, or neutral emotion [1]. The data were analyzed by a subtractive method, then, to clarify possible interactions among the regions within the brain, a correlation analysis was performed. Overall, significant activation was observed in the bilateral fusiform gyrus, medial temporal lobe, prefrontal cortex, and the right parietal lobe during the task. The results of subtraction between the conditions showed that the left amygdala, right orbitofrontal cortex, and temporal cortices were predominantly involved in the processing of negative expressions. The correlation analysis showed that the activity in the left amygdala positively correlated with the activity in the left prefrontal cortex under the negative minus neutral subtraction condition. These results suggest that the left amygdala plays a critical role in effective processing of negative facial expressions.

3. Implicit Processing of Facial Expressions and the Amygdala

Twelve healthy volunteers were asked to evaluate the facial expressions of a target face (500-ms duration) that expressed relatively weak anger [2]. Just before the presentation of the target face, a prime of three conditions of 35-ms duration, namely, an angry face, a neutral face, and a white blank image was presented. The subjects could not consciously identify the primes in this procedure. The subliminal presentation of the angry prime led to a greater activity in the right amygdala than subliminal presentation of a neutral face or a white blank image. Furthermore, the activation of the amygdala was positively correlated with the rate of judgment when the subjects recognized anger in the target faces. These results indicate that an implicit presentation of facial expression evokes amygdaloid activation.

4. Schizophrenia and the Amygdala

To investigate amygdala responses during facial recognition in schizophrenia, we conducted an fMRI study with 12 right-handed patients with schizophrenia and 12 age- and sex matched healthy controls [3]. During the task period, the subjects were asked to view happy (or angry/disgusting/sad) and neutral faces simultaneously presented at 3-s intervals and to judge which face was more emotional (positive or negative face discrimination). No significant difference in task accuracy was found between the schizophrenic and control groups. Positive face discrimination activated the bilateral amygdalae of both controls and schizophrenics, with more prominent activation of the right amygdala observed in the schizophrenic group. Enhanced amygdala activation during emotional intensity judgment found in the schizophrenic patients may reflect the impaired gating of sensory input containing emotion.

5. Serotonin Receptor Polymorphism and the Amygdala

To investigate the link between the 5-HT system and the limbic/prefrontal activity, normal subjects who underwent fMRI and face recognition tasks were genotyped for the single nucleotide polymorphism C178T in the regulatory region of the serotonin receptor type 3 receptor gene (*HTR3A*) [4]. We found that the subjects with C/C alleles exhibited greater activity in the amygdala and dorsal and medial prefrontal cortices than those with C/T alleles. The C/C group also showed a faster reaction time during the task than the C/T group. The temperamental predisposition of the subjects in the C/C group showed a significant correlation with brain activity. These results indicate that the C178T variation in the *HTR3A* gene has a critical influence on the amygdaloid activity and on human face processing, probably through the regulation of the receptor expression.

The present study may contribute to the elucidation of a possible link among genes, the brain, and behavior in normal populations, and may help to reveal the biological basis of neuropsychiatric disorders.

6. Emotion Regulation and Amygdala-Prefrontal Interaction

Recent neuroimaging studies have shown that several prefrontal regions play critical roles in inhibiting activation of limbic regions during voluntary emotion regulation. The healthy female subjects were presented with positive, neutral, and negative emotional pictures under the attending and suppression conditions [5]. Autonomic (skin conductance response: SCR) and hormonal (ACTH) indices were measured during the scanning. The left amygdala was activated under the attending condition, whereas activation was observed in the lateral, medial, and orbital prefrontal cortex under the suppression condition. Under the attending condition, the response in amygdala and prefrontal cortex positively correlated with magnitudes of the SCR and ACTH responses. These results suggest that the prefrontal cortex plays a pivotal role in top-down regulation of peripheral physiological responses accompanying emotional experiences.

7. Conclusion

Thus, studies pertaining to the human amygdala would greatly contribute to the elucidation of the neural system that determines emotional and stress responses. A focus of future studies is to reveal the functional interaction of the amygdala and other parts of the brain such as the prefrontal cortex. In particular, the medial prefrontal cortex has rich connections with the limbic region, and it is involved in the extinction of fear conditioning. An impaired response with respect to fear extinction is a biological model of anxiety disorder and posttraumatic stress disorder. To clarify the functional relevance of the limbic-prefrontal dysfunction and neuropsychiatric disorders, further studies using physiological, genetic, and hormonal approaches are essential.

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