SUMMARY OF THE DOCTORAL THESIS

TITLE:

Genetic and Neuroimaging Study of Anxiety-Oriented Temperament and Posttraumatic Stress Disorder

（不安志向性気質 および 外傷後ストレス障害に関する遺伝子・脳神経画像研究）

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Posttraumatic stress disorder (PTSD) is a mental disorder that exhibits three major symptoms more than one month after a traumatic event that entailed experiencing intense fear, horror, or a sense of helplessness. These three major symptoms are reexperience, avoidance or numbing, and hyperarousal. The psychopathology of PTSD is often understood as fear-conditioned responses to the traumatic event, from which it is difficult to extricate oneself. Recently, as with pharmacotherapy, psychotherapy has been suggested to act on the neurobiological basis contributing to the psychopathology of a mental disorder and to result in improvement of its clinical symptoms. However, little is understood about the neurobiological mechanism of psychotherapy for PTSD due to the critical problem that the neurobiological basis of PTSD remains unclear. Therefore, the present study aimed at revealing the neurobiological basis contributing to the psychopathology of PTSD.

In Study I-A, the relationship between the anxiety-oriented temperament of 'Harm Avoidance,' which is closely associated with PTSD, and gene polymorphism was investigated in healthy subjects. As the result, no significant relationship was found. This result and a comprehensive review of personality traits and gene polymorphisms by the author suggests that Harm Avoidance might be more directly influenced by the brain, for example, by its function or morphology, rather than by gene polymorphism. Thus, in Study I-B, the relationship between Harm Avoidance and brain glucose metabolism was explored in healthy subjects. Harm Avoidance was found to have a significant negative relationship with glucose metabolism in the medial prefrontal cortex which encompasses the anterior cingulate cortex and orbitofrontal cortex. Recent human and animal studies have suggested that these brain regions are engaged in the extinction of fear-conditioning. Moreover, functional activities of these brain regions are revealed to be reduced in PTSD patients with high Harm Avoidance scores. On the basis of these findings, the medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex were considered to play an important role as the neurobiological basis of PTSD as well as of Harm Avoidance. Therefore, in Study II, morphological alterations were examined in the brain of PTSD patients, focusing on the medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex. Morphological alteration, specifically smaller gray matter volume, was found in the orbitofrontal cortex of PTSD patients compared to comparison groups. Moreover, the smaller size of the orbitofrontal cortex was significantly correlated with greater intrusional responses to the traumatic experience. Recent neuroimaging studies among healthy subjects are gradually unmasking the function of the orbitofrontal cortex in the extinction of fear-conditioning and in the emotional retrieval of autobiographical memory. The

present work provides the first evidence of morphological abnormality of the orbitofrontal cortex in PTSD patients.

Psychotherapy for PTSD is known to be based on facilitating an extinctive learning of fear-conditioned responses and considerable evidence of its effectiveness has been accumulated. Given that the present findings indicate an important role of the orbitofrontal cortex in the psychopathology of PTSD, psychotherapy may improve PTSD symptoms through functional augmentation or structural fertilization of the orbitofrontal cortex of PTSD patients. Therefore, further investigation of the neurobiological mechanism of exposure-focused therapy concentrating on the orbitofrontal cortex is warranted. An understanding of the neurobiological mechanism of psychotherapy for PTSD will contribute to further improvement of existing clinical interventions or innovation of new therapies, as well as enable its application to the psychological treatment of other mental disorders in which enhanced stress responses to threat-related stimuli are often observed. In addition, such an understanding will be persuasive for improvement of current medical policy that does not cover psychotherapy by clinical psychologists.

In conclusion, the present work revealed the orbitofrontal cortex to play an important role as the neurobiological basis of the psychopathology of PTSD. The age of elucidating the neurobiological mechanism of psychotherapy for PTSD has just begun to dawn.