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Special Feature Article

Effects of Adverse Childhood Experiences (ACE) on Brain Development and Implications for Parenting Support

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Abstract

It has been widely recognized that adverse childhood experiences (ACE) increase the risk of subsequent maladjustment by adversely affecting numerous areas of cognitive development. In this study, we focused on child maltreatment as the primary childhood adversity experience and examined its effects on brain development during childhood. First, we reviewed the effects of maltreatment experiences on the brain for each brain area based on previous studies, and found reduced executive function in the prefrontal cortex, reduced hippocampal volume with secondary disorders, and dysfunction of the reward system. Next, we investigated the effects of the type and timing of child maltreatment on brain development based on our recent studies. The brain area affected was demonstrated to depend on the type and timing of maltreatment. This suggests different symptoms. Lastly, we reviewed the recent progress in neuroscience research related to parenting support. Based on the rapid development of brain function measurement technology, such as functional magnetic resonance imaging (fMRI), in recent years, we discussed the possibility of developing

a preventive model capable of early detection and intervention for mental illness and social adaptation difficulties, especially parenting difficulties. Further research on the prevention and intervention for parenting difficulties, and a better understanding of the mechanism of parenting will change the methodology for supporting parents, enabling the development of a support program in line with the diverse needs depending on individual differences in parenting skills and resources.

Keywords: adverse childhood experience (ACE), child maltreatment, brain, development, parenting support

Introduction.

It is well known that adverse childhood experiences (ACEs) increase the risk of later maladjustment by adversely affecting various developmental domains2) . For example, in the cognitive domain, ACE increases the risk of memory problems, learning difficulties, and delays in cognitive development, which may be related to academic difficulties and maladjustment in school.3)15)18) In addition, children with ACE often have difficulties in controlling their attention and behavior, and it has been suggested that this may be a risk factor for attention-deficit/hyperactivity disorder (ADHD) and problematic behavior18). It has also been suggested that ACE may be a risk factor for attention-deficit/hyperactivity disorder (ADHD) and problematic behaviors.18) In addition, atypical emotional and social development is often observed, which is associated with decreased sensitivity to rewards and difficulties in emotional control, as well as increased risk of developing psychiatric disorders, interpersonal problems, and involvement in antisocial activities.17)38) ACE has also been reported to pose significant health risks. In a large epidemiological study of 13,000 subjects, it was reported that the rates of smoking, suicide attempts, alcoholism, drug use, physical inactivity, and severe obesity were significantly increased.6) In Japan, child abuse has been reported to be associated with an increased risk of suicide. In Japan, it has been reported that the economic loss caused by child abuse is estimated to be at least 1.6 trillion yen per year in 2012.34) The social loss caused by ACE is immeasurable.

In the present study, we focus on the

effects of child abuse on brain development in childhood. First, we review the effects of abuse experiences on the brain based on previous research. Next, we examine the effects of the type and timing of abuse on brain development based on recent research conducted by the authors. Finally, recent advances in neuroscience research are outlined and future perspectives are proposed for the support of caregivers.

I. Effects of abusive experiences on the brain

It has been suggested that psychological stress caused by abusive experiences causes structural changes in brain regions important for stress response and emotion regulation (prefrontal cortex (PFC), hippocampus, amygdala, and reward system including striatum) by increasing cortisol in the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory cytokines in the immune system. The PFC plays a major role in the control of executive functions in cognitive, emotional, and stress responses.5) However, previous studies have shown that ACE caused by child abuse is associated with changes in the volume of the PFC. The PFC plays a major role in the regulation of executive functions in cognitive, emotional, and stress responses.5) However, previous studies have indicated that child maltreatment-induced ACE is associated with changes in PFC volume.16)31) Previous studies have indicated that ACE is associated with changes in PFC volume due to child abuse.16)31) It has also been reported that the size of PFC volume is a protective factor against the risk of developing psychiatric disorders and problematic behaviors due to the experience of abuse.14) Similarly, in terms of brain functioning, it has been reported that ACE is associated with changes in PFC volume due to child abuse.16) Similarly, it has been reported that the PFC is activated and its functional connectivity with other brain regions is altered in response to abuse11). The hippocampus is involved in emotion-based learning and memory, and has been the focus of previous studies examining the relationship between child abuse and brain imaging findings. Previous studies have focused on the relationship between child abuse and brain imaging findings. It has been reported that abusive experiences decrease hippocampal volume16)25)35) , and it has been suggested that small hippocampal volume may be a mediating factor for secondary disorders such as problematic behavior in childhood10) and depression in adolescence19) . In contrast, the hippocampal volume is larger in the

group of children who have experienced abuse but have not developed psychiatric disorders, suggesting that the hippocampal volume may be a marker for the development of psychiatric disorders caused by child abuse35). The amygdala plays a major role in the processing of emotional responses to threatening stimuli and has been examined in relation to child abuse35) , but recent meta-analyses have not found a clear relationship between the two16) . However, recent meta-analyses have not found a clear relationship between the two16) . On the other hand, brain function studies have consistently reported increased sensitivity to threat-related stimuli12) . This suggests that the effects of abuse on the amygdala may be manifested as changes in network parameters with other brain regions, rather than in structural parameters such as volume. Finally, previous studies have consistently reported decreased sensitivity of the reward system, including the striatum10)24) . Reward processing plays an important role in learning motivations and responses to sustain goal-directed actions, and is considered to be an essential function in building interpersonal relationships based on social rewards such as praise and in developing social skills. In previous studies, it has been suggested that decreased activity of the striatum due to an abusive experience is involved in subsequent interpersonal conflict and internalizing symptoms.4)24) As described above, we have reviewed the effects of abusive experiences on brain development by region (PFC, hippocampus, amygdala, reward system), but it will be necessary to clarify the effects on the network between each brain region. So far, there have been only a few studies on the effects of abuse experiences on the interregional network26) , and the detailed mechanisms have not yet been clarified. It is quite possible that structural, functional, and developmental imbalances in the interregional networks of the brain influence the symptoms and prognosis of child abuse.

II. Effects of the type and timing of abusive experiences on the brain

The incidence of psychiatric disorders caused by abusive experiences is known to vary depending on the type and timing of abuse. For example, in posttraumatic stress disorder (PTSD), 37.5% of victims of sexual abuse are reported to have PTSD, while 30.6% of victims of neglect are reported to have PTSD36) . The reason for this may be that the brain/endocrine system and genetic predisposition (vulnerability) involved differ depending on the type and timing of abuse. Because PTSD, as

well as other related stress disorders, depression, anxiety, and substance abuse (alcohol and drugs), can cause a wide variety of psychiatric disorders, it is difficult to determine the effects of the abuse experience on brain development. It is usually difficult to extract only the pure effects of abusive experiences on brain development. In order to exclude such effects as much as possible, the authors screened thousands of participants from the general public who had been exposed to only "one particular type of abuse" and examined the effects of the type and timing of abuse on subsequent brain development (gray matter volume) in a retrospective manner. The results showed a significant relationship between the type and timing of abuse. The results showed that, in relation to the type of abuse, psychological abuse by verbal abuse had an effect on the auditory cortex31) , whereas exposure to sexual abuse and domestic violence had an effect on the visual cortex29)32) , and severe corporal punishment had a significantly greater effect on the prefrontal cortex30) (Figure 1). In relation to the timing of the abuse, the effects differed depending on the timing as well as the type of abuse. In the case of sexual abuse in early childhood (3-5 years old), the effects on the hippocampus were relatively large, whereas the effects on the corpus callosum were relatively large in preadolescence (9-10 years old) and the frontal lobe in adolescence (14-16 years old).

In addition, child abuse is known to cause distortions in attachment formation with caregivers. In a recent study, the authors conducted a brain imaging study of children who had difficulty forming attachments with others due to their experiences of abuse7)20) . Reactive attachment disorder (RAD) occurs when child abuse interferes with the formation of stable attachments with caregivers. In this study, 21 children (mean age 12.8 years) with DSM-5 Magnetic resonance imaging (MRI) was performed on 21 DSM-5 diagnosed RAD children (mean age: 12.8 years) and 20 typically developing children (mean age: 12.7 years) to investigate the differences in gray matter volume between groups. Random forest regression was used to examine the effects of type of abuse and timing of exposure on gray matter volume in the RAD children only. The results showed that the gray matter volume of the visual cortex was significantly reduced by 20.6% in the RAD group compared to the typically-developing children20) , and that "neglect" and "number of overlapping types" of abuse had a significant effect on this reduction7) (Fig. 2a). In terms of the timing of

abuse, it was found that the experience of abuse between the ages of 4 and 7 years had a significant effect (Fig. 2b). Furthermore, in relation to clinical symptoms, a decrease in the volume of the visual cortex was significantly associated with anxiety, PTSD, and dissociative symptoms. Thus, the type of abuse and the timing of the abuse experience greatly influence subsequent brain development, which in turn leads to a variety of clinical symptoms. By taking a tripartite approach based on the relationship between the type of abuse, timing of exposure, clinical symptoms, and brain imaging findings as intermediate phenotypes, it is possible to understand the importance of non-uniform interventions, the difficulties in building interpersonal relationships and reestablishing attachment to caregivers caused by child abuse, and the pathogenesis of related psychiatric disorders such as PTSD. It will also contribute to the understanding of the pathogenesis of related mental disorders such as PTSD and the development of treatment and support methods.

III. Advances in Brain Science Research Leading to Support for Caregivers

Children's development is guided and supported by their relationships with caregivers and others around them. Understanding the psychological adaptations of caregivers who guide and support children's development and nurture them together is useful for maintaining and promoting the parent-child relationship and for gaining a perspective on its breakdown (pathology). In particular, when a child has developmental problems, attachment to the caregiver is delayed, and trauma in the nurturing environment (e.g., experiences of abuse) or social life (e.g., experiences of bullying at school) is easily brought in. It can be said that the process of relationship development between caregivers and children is also uneven, but even the most caring caregivers are considered to be at risk of falling into child-rearing difficulties and disorders (worst case scenario: abuse or suicide) due to the accumulation of not only physical fatigue but also invisible mental fatigue. Serious problems in child-rearing do not occur suddenly, but rather progress through the four stages of child-rearing functioning: preparation for child-rearing, healthy child-rearing, child-rearing difficulties, and child-rearing failure (Fig. 3).22) In order to maintain and promote healthy child-rearing and to prevent serious problems in child-rearing, it is necessary to construct and develop a preventive child-rearing support

system according to the stages. Recent brain research has shown that the effects of these factors also appear during the first two years of life (the most rapid period of brain development and critical for the development of children's later mental functions). However, recent brain research has revealed that these effects are also manifested during the first two years of life (the most rapid period of brain development in children and critical for later mental development).8)

As an adaptation of the caregiver's mind that produces prosocial nurturing behavior, it is known that the caregiver's sensitivity to social signals (signals) such as infant crying increases28) . It is believed that caregivers (mothers), unlike non-caregivers, are able to detect social signals such as crying efficiently by continuously allocating their attention to the infant's condition. Brain research on the neural basis of such nurturing abilities9) has shown that nurturers increase the activity of the insular cortex and inferior frontal gyrus when processing social signals compared to non-nurturers. This brain function helps caregivers to efficiently detect social information from others around them, thereby protecting their children from danger and increasing their chances of survival. However, caregivers who suffer from mental health problems triggered by the accumulation of stress in child-rearing may experience a decline in their ability to care for their children, which in turn may lead to a decline in the functioning of their neural infrastructure. It has been reported that depressed caregivers have reduced activity in brain regions such as the striatum when listening to infant crying compared to healthy caregivers13) . 13) This decrease in nurturing brain function is inversely correlated with the severity of depressive symptoms, which is more severe in caregivers with more severe depressive symptoms, suggesting that it is related to the problem of sensitivity to social signals from infants. On the other hand, there are many reports that parent training for caregivers with such child-rearing difficulties reduces child-rearing stress and improves child-rearing skills. Although it is not fully clear whether the training is effective in improving the decline in nurturing brain function, a limited number of brain studies23) have reported that parental training improves nurturing brain function.

In a recent brain study21) , functional magnetic resonance imaging (fMRI) was used to examine the stress vulnerability of the neural substrates involved in social competence in healthy caregivers (mothers) of

preschool-aged children. In the fMRI experiment, the target caregivers were asked to perform a social competence task in which they had to guess the feelings of others, either adults or children. The caregivers were presented with a photograph of an adult or a child as an experimental condition, and were asked to guess the emotional state expressed by the person in the photograph and to choose an emotional word to answer the question. In the control condition, the participants were asked to judge the gender of the person in the photo and to choose a gender word as their answer. Based on the difference in brain activity between the experimental and control conditions, the activity values of brain regions selectively involved in the ability to infer the feelings of others were estimated, and the correlation between these values and indicators of depressive tendencies such as the depressed mood of caregivers was analyzed. The results showed that caregivers with higher depressive tendencies showed more decreased activity in the right inferior frontal gyrus, which is involved in the ability to guess the feelings of adults, but no decrease in activity in the brain region involved in the ability to guess the feelings of children (Fig. 4). Neither task performance (e.g., percentage of correct answers) was correlated with depressive tendency, nor did it decrease. The cognitive-behavioral index of the ability to infer the feelings of adults was maintained in the accumulation of mental fatigue in caregivers in the healthy upbringing stage (but not in depression), but the activity of the right inferior frontal gyrus, which is part of the neural infrastructure involved in this ability as a functional index of the brain, was reduced. It can be said that co-parenting with surrounding adults in a nurturing environment prevents child-rearing isolation and reduces burden and anxiety, but phenomena such as a decline in social brain function associated with an increase in depressive tendencies are not only signs that precede the severity of the caregiver's own mental fatigue (e.g., depression), but are also signs of interpersonal problems with surrounding adults (e.g., emotional problems). This is a sign that can lead to problems in interpersonal relationships with the adults around them (e.g., emotional conflicts), and can contribute to the development of preventive indicators of child-rearing difficulties and disorders. If such research and development progress, it will be possible not only for caregivers to become aware of their own emotional exhaustion in the process of developing relationships between caregivers and children, but also for caregivers to

share their emotional exhaustion objectively and quantitatively with surrounding supporters, leading to the prevention of isolation and difficulties in child-rearing.

In recent years, the development of biomarkers for psychiatric disorders using brain function measurement techniques such as fMRI has been rapidly progressing in conjunction with interdisciplinary collaborations with computational neuroscience and other fields, but according to a recent report37) , the scope of this research has been largely limited to the development of diagnostic models. For example, research on the development of brain function indices (preventive models) that predict the severity of depressive tendencies in caregivers (prodromal state of depression) is limited to a few percent, and further progress in the development of preventive models that can detect and respond to mental disorders and related social adjustment difficulties (child-rearing difficulties, etc.) at an early stage is desired. In the future, a deeper understanding of the mechanisms of nurturing brain functions and further research on the prevention of and intervention support for nurturing difficulties and associated declines in nurturing brain functions will lead to a change in methodology for supporting caregivers and will make it possible to construct support programs that meet diverse needs, including individual differences in nurturing abilities. This will lead to methodological changes in supporting caregivers and enable the development of support programs that meet diverse needs, including individual differences in nurturing abilities. The development of basic and applied multidisciplinary research, including brain science research, for supporting caregivers and its application to society will lead to the updating of the awareness and attitudes of all members of the community, including child-rearing supporters, toward child-rearing, and create an environment in which caregivers can rely on and consult with all members of the community for the care of their children. It is hoped that this will lead to the creation of an environment where caregivers can rely on and consult with others in the community for the care of their children.

Conclusion.

In this article, we have reviewed the effects of abusive experiences on brain development as one type of ACE from the perspective of neuroscience and neuroscience research that leads to support for caregivers, but the corresponding relationships have not yet been systematically clarified. In order to scientifically understand the

effects of ACE on brain development, it is necessary to consider brain development from the perspective of "ecophenotype.) Neuropsychiatric symptoms associated with child abuse may include hyperactivity, impulsivity, and difficulties with emotional control, which are similar to the traditional criteria for neurodevelopmental disorders. The neurological basis and genetic background of a patient with a psychiatric disorder who has a history of severe abuse in childhood should be different from that of a patient with the same diagnosis who has no history of abuse. Developmental problems in the context of child abuse are associated with younger age of onset, poorer course, more multiple diagnoses, and slower response to initial treatment. Awareness of these differences would increase the overall effectiveness of treatment and promote basic biological research in psychopathology. The "ecological phenotype" is based on this idea. While adaptation to the environment is an essential strength for children to survive, the impact of the environment on children is significant. In order to protect the physical and mental health of children, who will be the leaders of the next generation, and to promote their better development, treatment and support based on scientific evidence of brain development will become increasingly important in the future.

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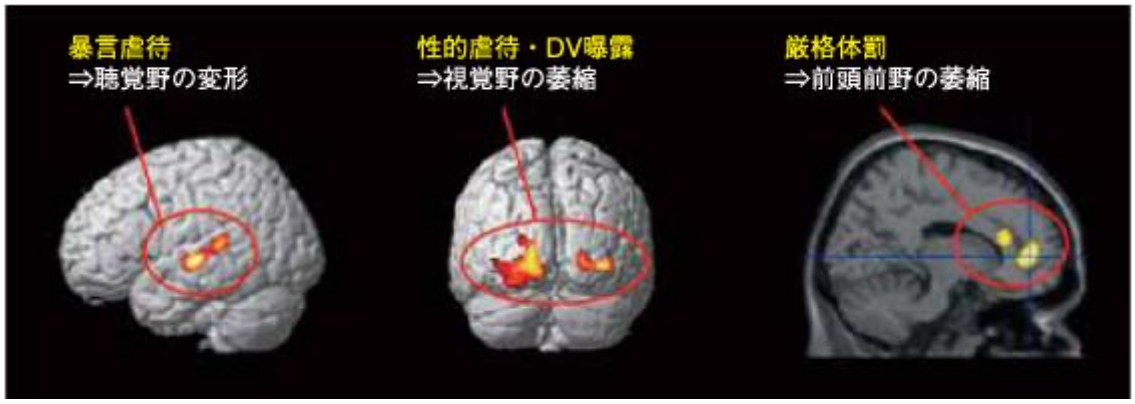

Fig. 1 Various effects of exposure to child maltreatment on brain volume.
(Modified from ref. 33)

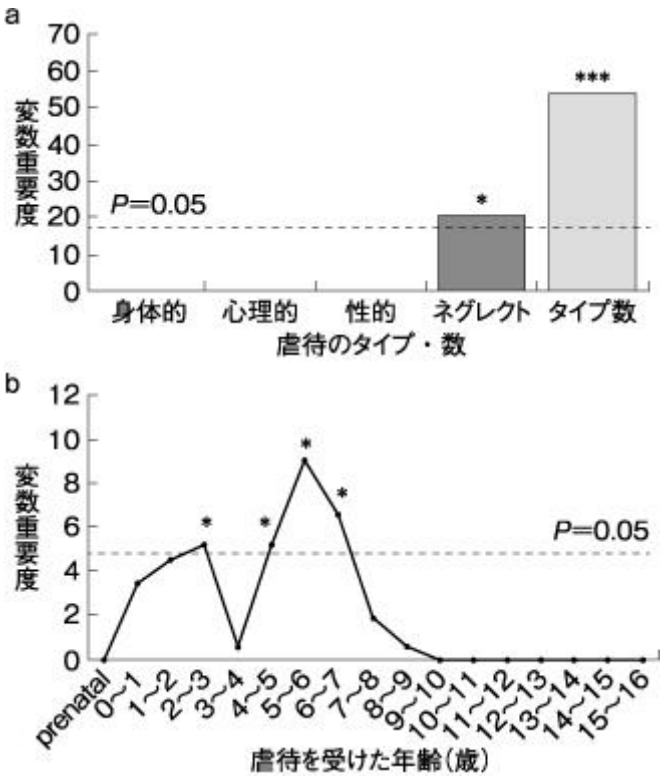

Fig. 2 Estimated variable importance of the effects of type and timing of maltreatment exposure on volume loss in the visual cortex.
P<0.05, **P<0.001, FDR-corrected
(Adapted from ref. 7)

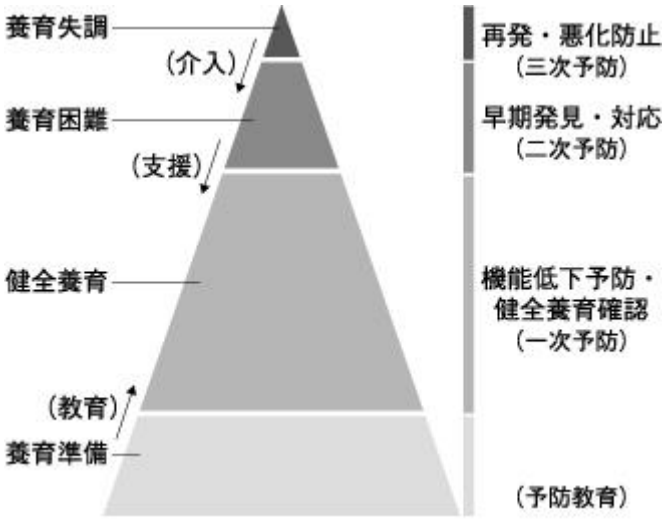

Figure 3: Progression and prevention model of parenting dysfunction.
(Adapted from Reference 22)

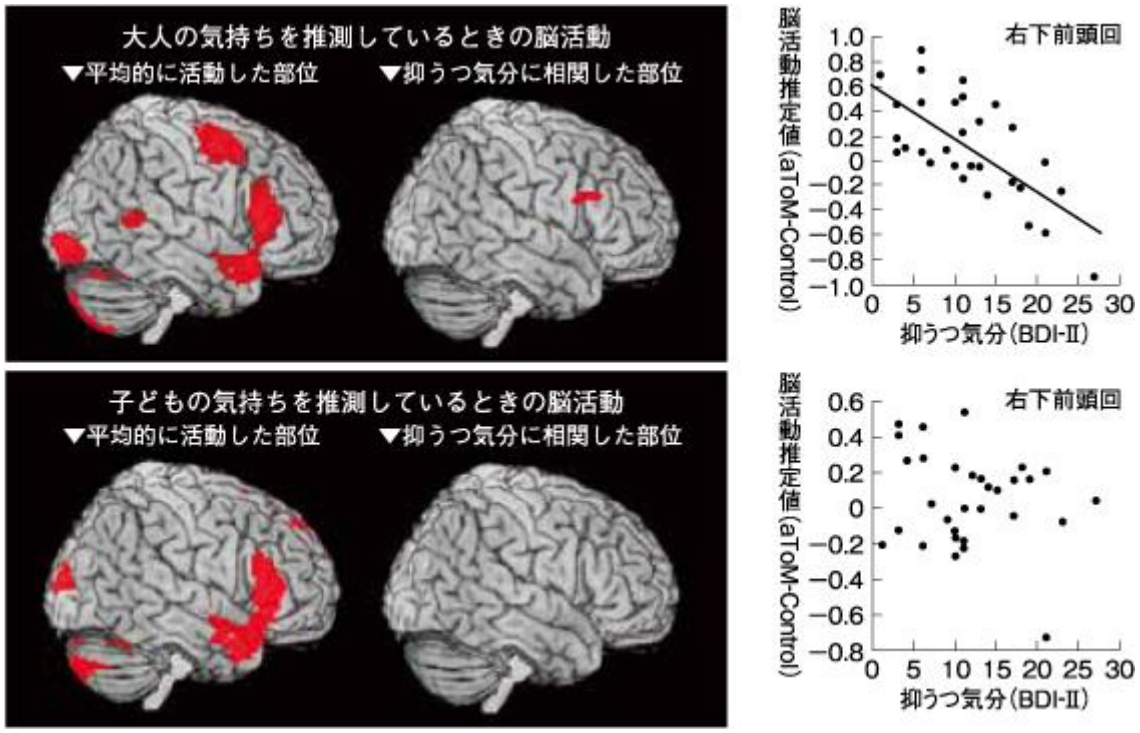

Fig. 4 Brain regions recruited among mothers overall in response to the adult eyes-based and infant face-based mind-reading tasks (Right hemisphere)
BDI-II: Beck Depression Inventory II
(Adapted from Reference 21)