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Age-related White Matter Structural Changes Revealed by Whole-brain Fiber Tracking Method in Patients with Bipolar Disorder, Depression, and Healthy Controls

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Abstract

Recent diffusion tensor imaging (DTI) studies have shown relatively consistent findings of decreased white matter integrity in those with mood disorders, but it has been pointed out that depression and bipolar disorder share many of the same white matter regions that show decreased integrity and that the altered regions are not disease-specific. However, there are no reports directly comparing depression and bipolar disorder, and it is not clear whether there is a disease-specific relationship between age and decreased white matter integrity in the two disorders. Therefore, we directly compared white matter integrity of the two disorders after adjusting for age effects. In this paper, we present the results of our study. DTI was performed for 58 subjects with bipolar disorder, 101 subjects with depression, and 98 healthy controls, and the images were analyzed by whole-brain fiber tracking. A test for age-group interaction was performed. Major white matter fiber regions showed a main effect of age on FA values, and FA values decreased with age in all regions. Among these regions, a main effect of group was found in the left body of the corpus callosum and left column and body of

the fornix, and post-tests showed a significant decrease in FA in bipolar disorder compared with depressed subjects and healthy controls. No age-group interaction was found in any of the white matter fiber regions. These results suggest that bipolar disorder may have already caused white matter hypointegration in the left body of the corpus callosum and left column and body of the fornix in the early stages of the disorder.

Keywords: diffusion tensor imaging, cerebral white matter, change over time, depression, bipolar disorder

Introduction

Diffusion tensor imaging (DTI) is an MRI technique that noninvasively evaluates fine white matter structures by quantifying the diffusion of water molecules in vivo[15]. Recent large-scale DTI studies showed consistent findings of decreased white matter integrity in patients with bipolar disorder[7)20)22)] and depression[2)3)11)17)30)]. On the other hand, most of the hypointegration is found in common white matter fiber areas, and the disease specificity between the two disorders has not been fully clarified. In addition, it is known that white matter integrity in normal subjects increases until the late thirties and then declines in a quadratic manner with age[13)]. In schizophrenia[4)14)31)], it has been shown that this change in white matter integrity over time differs from that in normal subjects, and a large cohort study by the ENIGMA MDD Working Group reported that even in depressed patients, the decline in integrity accelerated with age in the genu of the corpus callosum, the body of the corpus callosum, the fornix/stria terminalis and the sagittal stratum. (inferior fronto-occipital fasciculus and inferior longitudinal fasciculus), and an accelerated decline in integrity with aging compared with normal subjects has been reported[27)]. On the other hand, in patients with bipolar disorder, it has been reported that the age-related decline in integrity accelerates in the uncinate fasciculus, hippocampal portion of the cingulum and the genu and splenium of the corpus callosum [5)26)], and in addition, a decline in white matter integrity in the corpus callosum and inferior longitudinal fasciculus can already be observed in younger age groups in their 20s and 30s, suggesting the possibility of dysplasia of white matter structures[28)]. Thus, when we look at the relationship between age

and white matter integrity decline in psychiatric disorders, two mechanisms can be postulated: (1) white matter integrity decline already occurs at a young age, and (2) white matter formation proceeds as in normal subjects, but the decline progresses rapidly after disease onset. Although examining how age influences white matter integrity may be important for a better understanding of white matter structural changes, there have been no reports directly comparing changes in white matter integrity over time in subjects with bipolar disorder and depression, and it is not clear whether there is disease-specificity in the relationship between changes in white matter integrity and age between the two disorders. Therefore, we directly compared the white matter structures of the two diseases after adjusting for age effects, clarified the differences, and examined the relationship between white matter integrity and age[19]. In this paper, we present the results of our study.

I. Methods and Results

1. Subjects and Methods

Patients with bipolar disorder (58 subjects, age range: 22-76 years, mean age: 52.0±12.5 years, duration of illness: 1-51 years, mean duration of illness: 17.4±11.1 years) and patients with depression (101 subjects, age range: 25-78 years, mean age: 50.5±13.2 years, duration of illness: 1-37 years, mean duration of illness: 7.6±7.3 years) and healthy controls (98 subjects, age range: 20-77 years, mean age: 53.7±13.2 years). All patients were in the depressed or remission phase and receiving medical treatment at the time of imaging. This study was conducted in accordance with a protocol approved by the Ethics Committee of Hiroshima University, with full informed consent, confidentiality, and anonymity preserved.

DTI was performed using Siemens 3 Tesla MAGNETOM Verio. Imaging parameters were TR (repetition time)/TE (echo time): 8,100/94 ms, b-value: 1,000 s/mm2, MPG (motion probing gradient): 30 axes, field of view: 240 × 240 mm2, voxel size: 2.5×2.5×2.5 mm3, image matrix=96×96. Brain images were analyzed according to the whole-brain fiber tracing method of Okuhata et al.[21]. Based on the brain white matter atlas provided by Johns Hopkins University, the major white matter fiber regions were divided into 54 left and right areas, and fiber tracing was performed on all of these areas. Fractional anisotropy (FA) values, which indicate diffusion anisotropy, were calculated as an indicator of white matter integrity. The white matter regions with a group main effect were determined using a generalized linear

model with the FA value of each region as the response variable and age and group as explanatory variables, and an age-group interaction test was also conducted. Multiple comparison tests were performed for the white matter regions with group main effects. The same model was used to test the duration of disease group as an explanatory variable, and the duration of disease group interaction was tested using the Bonferroni correction for multiple comparisons at a significance level of P=0.05/54=0.00093. Sex, stage of disease, and drug load index were used as covariates.

2. Results

The effects of age and group on FA values showed a main effect of age on FA values in all groups in several white matter fiber regions including the corpus callosum, and FA values decreased with age in all groups. The main effects of group were found in the left body of the corpus callosum (P<0.001) and the left column and body of the fornix (P<0.001), and post-tests showed a significant decrease in FA in patients with bipolar disorder compared with depression and healthy controls. On the other hand, no age-group interaction was noted in any of the white matter fiber regions (Figures 1, 2) [19]. Neither the duration of disease, main effect of group, nor duration of disease-group interaction was observed in any of the white matter fiber regions.

II. Discussion

The results of this study showed that bipolar disorder significantly reduced white matter integrity in the left column and body of the fornix and the left body of the corpus callosum with depression and healthy controls, and that there was a main effect of age in these regions, but no interaction effect. No main effect or interaction was found for duration of illness. These results suggest that white matter integrity is reduced in the early stages of bipolar disorder in the left column and body of the fornix and the left body of the corpus callosum. Although the pathogenesis of white matter hypointegration in psychiatric disorders remains unclear, two hypotheses have been proposed: the vulnerability model postulates that there is a genetic vulnerability related to neurodevelopment, resulting in dysplastic white matter structures before or early in the stage of disease onset, and the neurotoxicity model postulates that biochemical changes such as high cortisol levels and neuroinflammatory activity after onset have neurotoxic effects on glial cells and the myelin sheath, resulting in decreased integrity as the disease progresses[23]. The present results, which showed decreased white matter

integrity in the early stages of bipolar disorder, suggest that decreased white matter integrity in bipolar disorder may be explained by the fragility model. Genetic studies have indicated that genetic mutations in DISC1 and Neuregulin 1 (NRG1), which are important in the process of myelin sheath formation, may be involved in the pathogenesis of bipolar disorder[12], and further research on genetic involvement in the developmental mechanism of reduced white matter integrity is expected. Both the fornix and the corpus callosum are commissural fibers that connect the left and right hemispheres, and commissural fibers are known to mature earlier than association and projection fibers. In particular, the fornix begins to form in infancy and early childhood, and reaches its peak FA value before the age of 20, making it the most rapidly maturing white matter region among white matter fiber regions[9][16]. This study suggests that reduced white matter integrity in patients with bipolar disorder may preferentially occur in early-maturing white matter fiber regions. The corpus callosum is the largest white matter structure that communicates between homologous cortices of the left and right cerebral hemispheres and transfers and integrates information between hemispheres[8][16]. The fornix is a commissural and projection fiber located in the medial part of the cerebral hemispheres and constitutes the main centrifugal nerve of the hippocampus[6][25]. Reduced integration of these commissural fibers is considered to decrease the efficiency of information transfer between hemispheres. In his model of emotion processing, Shobe [24] describes the importance of coordinated hemispheric activity via commissural fibers, in which the right hemisphere directly mediates the identification and understanding of pleasant and unpleasant emotional stimuli, and information about the emotion is shared with the left hemisphere via the corpus callosum. Inefficient information transfer between the hemispheres in bipolar disorder may interfere with the exchange of emotion-related information and lead to emotion dysregulation[33]. In addition, the corpus callosum and cerebral arches are considered to be involved in cognitive functions such as working memory, problem-solving, and memory[1][25][34][34]. Both depression and bipolar disorder are known to involve cognitive dysfunction in a wide range of domains, but a meta-analysis of both disorders reported that domains such as attention and memory are more severely impaired in bipolar disorder[10][29][32]. In our study of white matter integrity and cognitive

function in depression and bipolar disorder[18], we suggested that decreased white matter integrity in the corpus callosum in the presence of bipolar disorder was associated with impaired attention maintenance. The fact that white matter integrity in the corpus callosum of bipolar disorder is reduced at an earlier stage than that of depression, and that the degree of reduction is associated with attentional dysfunction, are important findings to understand the etiology and pathophysiology of both disorders; however, further validation is needed.

Conclusion

This study used a cross-sectional design, comparing the association between each age group and white matter integrity in bipolar disorder and depression as a method of assessing changes in white matter integrity over time; however, a longitudinal study that continuously follows the same subjects is considered necessary to validate this finding. Although the whole-brain fiber tracing method allowed us to comprehensively evaluate major white matter fiber areas, the sample size was not sufficient, and the influence of clinical background factors such as stage of disease, medications, severity of disease, and number of episodes could not be fully investigated. Furthermore, the functional significance of changes in white matter integrity over time needs to be investigated. We are already collecting longitudinal data at our institution, and we intend to examine the influence of background factors and their clinical significance as we continue our longitudinal study.

We have no conflicts of interest to disclose in connection with this article.

This article is based on a recent research article[19] published in PCN, which was rewritten in Japanese by one of the authors at the request of the editorial board, with additions on the significance and prospects of the article.

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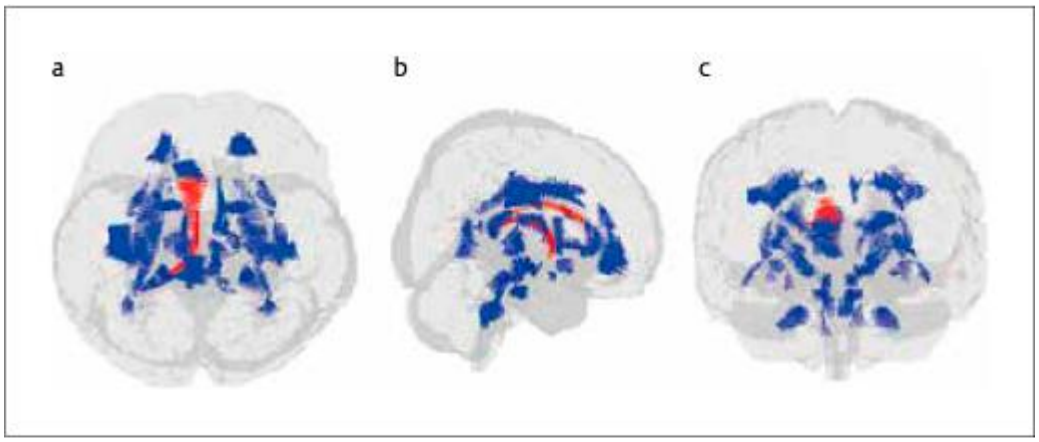

図 1　双極性障害群，うつ病群，健常対照群で群間差のみられた白質線維領域
青色の箇所は全脳線維追跡法を行った全体の白質線維領域を示し，赤色の箇所は双極性障害でうつ病と健常対照群と比べて FA 値の低下していた左側脳梁体部，左側脳弓体部/柱部を示す．
（文献 19 より和訳して引用）

Figure 1 White matter fiber areas showing group differences among bipolar disorder, depression, and healthy control groups.
The blue areas indicate the whole white matter fiber regions where whole brain fiber tracing was performed, and the red areas indicate the left body of the corpus callosum and left column and body of the fornix where FA values were lower in patients with bipolar disorder than depression or healthy controls.
(Adapted from reference 19)

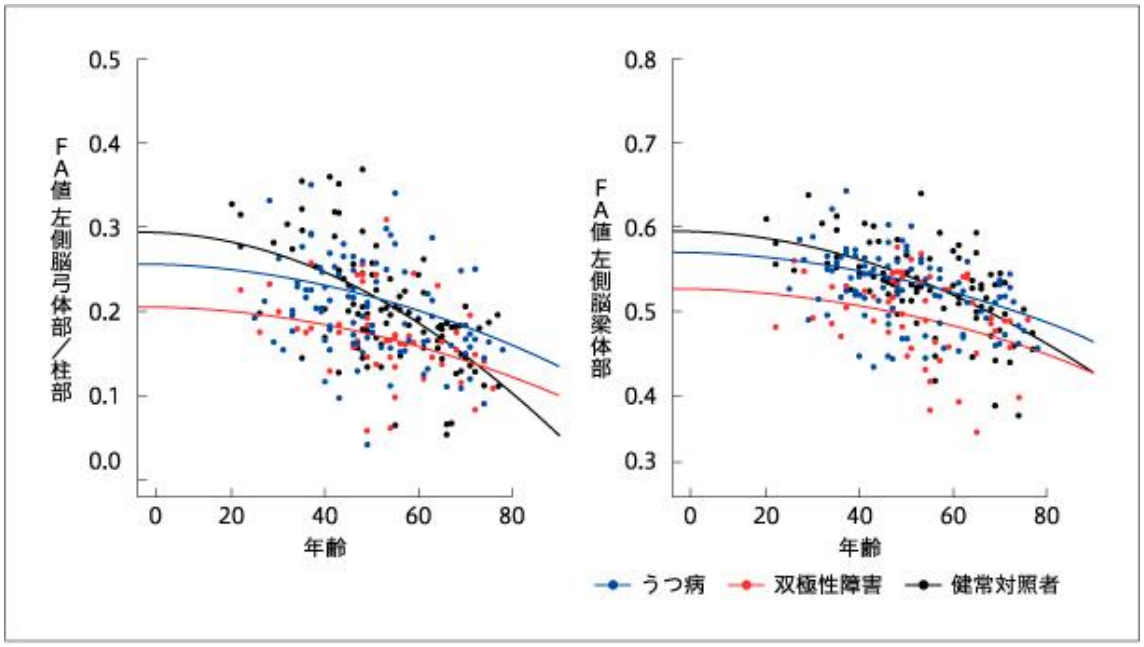

図 2　左側脳梁体部，左側脳弓体部/柱部の FA 値と年齢との関係

両白質線維領域とも双極性障害（赤色）はうつ病（青色），健常対照群（黒色）と比べて FA 値が有意に低く，年齢との間に二次曲線的な関係性がみられたが，年齢-群交互作用はみられなかった．
（文献 19 より和訳して引用）

Figure 2: Relationship between FA values and age in the left body of the corpus callosum and left column and body of the fornix.

In both white matter fiber regions, FA values were significantly lower in patients with bipolar disorder (red) than depression (blue) or healthy controls (black), showing a quadratic relationship with age, but no age-group interaction.
(Adapted from reference 19)