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Original Research Paper

Decreased Cross-Sectional Area of The Anterior Thalamic Peduncle In Bipolar Disorder: A Fiber Tracking Study

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Abstract: There is a hypothesis that impaired integrity of white matter is involved in the pathology of bipolar disorder. The anterior thalamic peduncle is a nerve fascicle connecting the thalamus and the prefrontal region, and it might be related to the cognitive impairment of bipolar disorder. In this study, we acquired diffusion tensor images from eleven bipolar patients and fifteen healthy persons. Fiber tracking was performed on the anterior thalamic peduncle, and tractographs were drawn up. The cross-sectional area (CSA), mean fractional anisotropy (FA), and mean apparent diffusion coefficient (ADC) were assessed and compared between the patient group and the control group. Compared to the healthy persons, bipolar patients had a significantly smaller CSA in the right and left anterior thalamic peduncles. No significant differences were seen between the groups in terms of ADC and FA. In both groups, CSA, FA, and ADC for the left side showed significantly higher values than for the right side. These findings may represent a disruption in white matter integrity between the thalamus and prefrontal cortex in bipolar disorder. Further, bilateral neurodevelopmental impairment may be closely involved in the pathology of bipolar disorder.

Keywords: anterior thalamic peduncle, bipolar disorder, diffusion tensor imaging, fiber tracking, white matter

1. Introduction

Advances in neuroimaging technology have made it possible to show structural abnormalities of functional psychiatric illnesses. Bipolar disorder is one such psychiatric disease, along with schizophrenia, in which neuroanatomical abnormalities are reported the most frequently. In their case report, published in 1987, Dupont and his colleagues described how MRI T2-reinforced images detected subcortical white matter hyperintensities in bipolar patients[1]. Numerous clinical studies were subsequently carried out using a large number of patients [2-6], and white matter hyperintensities have become one of the most replicated neuroimaging findings in bipolar patients [7]. However, their clinical significance remains largely unclear.

On the other hand, functional imaging studies of bipolar disorder showed a dysregulation of prefrontal activity in bipolar patients with mania [8-10], decreased activation in the prefrontal cortex in bipolar patients with depression [11-13], and enhanced subcortical activation in the amygdala, thalamus, and basal ganglia with depression and mania[14, 15]. However, an overwhelming number of morphometric studies of thalamus using MRI state that no volume changes are seen in bipolar disorder[16]. Regarding the prefrontal cortex, although numerous studies on bipolar disorder using MRI have indicated a decrease in the volume of prefrontal region [17-20], there are also reports claiming that no volume reductions were seen [21, 22]. A recent meta-analysis of brain morphometry using robust threshold criteria for inclusion suggested that bipolar patients as well as controls had similar bilateral prefrontal volumes [23]. Prefrontal volume reduction therefore remains an unresolved issue.

Considering these findings, it is hypothesized that the disruption of fronto-thalamo connectivity, which is involved in cognitive function and affects regulation, may be responsible for the core mood symptoms in bipolar disorder [24]. Expectations are being placed on studies of white matter and its integrity using diffusion tensor imaging (DTI) as a means of validating this hypothesis [25].

DTI is a non-invasive method of measuring the

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diffusion phenomenon of water molecules *in vivo*. In cerebral white matter, diffusion in the same direction as nerve fibers is rapid, whereas diffusion perpendicular to them is slow. By qualifying and quantifying the detection of the nerve fibers that run through the white matter, it is possible to detect structural abnormalities [26].

Buchsbaum and his colleagues investigated fronto-thalamo-striatal connections in patients with bipolar spectrum illnesses as compared to normal controls [24]. With regard to fronto-thalamo connectivity, they reported a reduced volume of the white matter of the frontal cortex in bipolar patients, and no between-group alterations in anisotropy in the anterior limb of the internal capsule. However, this study was carried out using the region-of-interest (ROI) method. In this method, the findings are not necessarily comparable, since the results depend on how the ROI is selected. Therefore carrying out fiber tracking on the specific fiber bundles connecting the thalamus and the prefrontal region, and detecting abnormalities of fronto-thalamo connectivity, will help elucidate the anatomical and functional dysfunction of bipolar disorder. In this study, we conducted fiber tracking, targeting the anterior thalamic peduncle, which is a nerve fascicle that runs from the thalamus toward the frontal lobe, especially the dorsolateral prefrontal cortex, by way of the anterior limb of the internal capsule. Using tractography-based ROI, a method for conducting a comparative study based on pertinent tractography, we investigated the cortico-subcortical network abnormalities of bipolar disorder.

2. Methods

2.1 Subjects

Prospective patient subjects were selected from outpatients who visited Kyorin University Hospital Clinic for treatment between January 2007 and December 2007. The inclusion criteria were bipolar disorder of DSM-IV [27], and ages between 20 and 45 years. The exclusion criteria were co-morbid axis I disorders, presence of axis II disorders, organic brain diseases, or diabetes mellitus. Healthy volunteers were recruited for the normal comparisons. Assessments for patients and comparison subjects were made through direct interviews by expert clinicians. The consent form and the research protocol were approved by the Institutional review board of Kyorin University Hospital. Patient and healthy control subjects reviewed the consent form and gave written informed consent in the presence of a study physician before participation. Subsequently, 11 patients (6 females and 5 males) meeting the inclusion criteria along with 15 healthy controls with no history of psychiatric disorder (8 females and 7 males) were selected for the study. Of the eleven patients, 5 had bipolar I disorder, and 6 bipolar II disorder. There were no significant differences in age or sex composition between the patient and control groups. One of the eleven patients was not taking any medications at the time of enrollment. Ten patients were taking medication. All patients taking medications were euthymic, and the one drug-free patient was depressive when they were MRI-scanned. Baseline demographic characteristics of the whole sample are presented in **Tables 1 and 2**, respectively.

Table 1 Subject demographics

Group	Bipolar patient (N=11)	Healthy control (N=15)
Age (years)	34.9 ± 5.6	32.5 ± 6.0
Male/Female	5/6	7/8
Handedness (R/L)	11/0	15/0
Age at disease onset (years)	30.3 ± 7.3	-
Duration of illness (year)	4.6 ± 4.1	-

Age, age at disease onset, and duration of illness presented as mean years ± SD.

Table 2 Patient data

Subject	Age (years)	Sex	Duration of illness	Medcation(s) being taken at (months) time of the MRI scan
1	30	M	43	lithium, valproate, zotepine
2	39	F	52	amoxapine
3	35	F	181	lithium, milnaciplan
4	29	F	9	lithium, olanzapine
5	35	F	4	none
6	42	M	74	lithium
7	37	F	60	lithium, risperidone, fulvoxamine, mianserine
8	24	F	92	carbamazepine, zotepine, haloperidol
9	35	M	34	valproate, risperidone, fulvoxamine
10	35	M	47	lithium, risperidone
11	43	M	15	valproate, paroxetine

2.2 MRI protocol and fiber tracking

Imaging was performed on a 1.5 Tesla Intera Achieva Nova Dual MRI Scanner (Philips Medical Systems, Best, Netherlands). The parameters were set as follows: TR 2900 ms, TE 60 ms, NEX (the number of excitations) 6, FOV (field of view) 240 mm, voxel size 1.88 x 1.88 x 5.0 mm^3, image matrix 128 x 128, slice thickness 5 mm, 25 slices. MPG 6 directions ([0.3333, 0.6666, -0.6666], [0.6666, 0.3333, 0.6666], [-0.6666, 0.6666, 0.3333], [0.7071, 0.7071, 0], [0, 0.7071, 0.7071].

[-0.7071, 0, 0.7071]), b-value 1000 s/mm^2. For quantification of fractional anisotropy (FA), Basser's method [28] was used.

Our study targeted the anterior thalamic peduncle, which is a nerve fascicle that runs from the thalamus toward the frontal lobe by way of the anterior limb of the internal capsule. To set the ROI in the target nerve bundle, we first established the cross-section of the internal capsule in the coronal section that includes the anterior commissure (xz plane) as the starting region for fiber tracking, and then we established the coronal section that includes the anterior genu of the corpus callosum as the ending region for fiber tracking. Each of these starting and ending regions in the right and left hemispheres were moved separately back and forth within a range of 8 mm, after which fiber tracking was performed. The sites where the largest number of streamlines could be tracked were finally selected as the starting and ending regions for the fiber tracking, and, based on them, tractography was applied. In identifying the fiber tracts in the region of interest, we dispersed the tracking starting points evenly on the plane of the starting region at a rate of 4 points/mm^2. For fiber tracking, the Streamlines Tracking Technique [29-31] and the Runge-Kutta Fourth Order Method [32] were used, while the step width was made 0.5 mm. Fiber trajectories were terminated at the voxel with FA less than 0.25 or when the turning angle between adjacent steps was greater than 45 degrees. To identify and erase erroneously tracked fibers, out of the extracted fiber groups, we separately selected for the right and left hemispheres, the one whose fiber length was the shortest, and used that length as the baseline fiber length. Any fiber measurement for which the length exceeded 105% of the baseline fiber length was judged to be an erroneous tracking result and it was eliminated from the fiber group. From the tractographs, the cross-sectional area (CSA) of the nerve fascicles in the starting region, the average FA of the nerve fascicles, and the average apparent diffusion coefficient (ADC) of the nerve fascicles were calculated separately for the right and left hemispheres in the both groups. Creation of tractographs, and quantification of the CSA, average FA, and average ADC were done using the Matlab 7.1 program created by two of us, Jung and Kobayashi.

2.3 Statistical analysis

Statistical analysis was performed by using SPSS for Windows 14.0J (SPSS Inc., Tokyo, Japan) and the level of statistical significance was set at $p<0.05$. Two-way repeated analysis of variance (ANOVA) with between-groups and within-subjects (hemisphere) were made for CSA, FA, and ADC values in the anterior thalamic peduncle. In the case of significant group-by-hemisphere interactions along with significant between-group effects, or between-hemisphere effects, t-tests were used to compare group and hemisphere asymmetry differences respectively.

3. Results

Table 3 shows CSA in the starting region, average FA, and average ADC of the anterior thalamic peduncle of the 11 patients and 15 healthy controls. The anterior thalamic peduncle in the right hemisphere could not be traced in one patient.

For CSA, ANOVA showed significant between-group effects for patients and comparison subjects, significant between-hemisphere effects, and no significant group-by-hemisphere interactions. For FA and ADC, ANOVA showed significant between-hemisphere effects, no significant between-group effects, and no significant group-by-hemisphere interactions. As for CSA, FA, and

Table 3 Subject data

Group		Bipolar patient (N=11) mean ± SD	Healthy control (N=15) mean ± SD	ANOVA					
				Group effects		Hemisphere effects		Interactions	
				F (df=1, 23)	p	F (df=1, 23)	p	F (df=1, 23)	p
Cross-sectional Area (mm^2)	Left	13.66 ± 15.66	32.12 ± 20.12	6.92	0.015	7.36	0.012	1.05	0.315
	Right	9.30 ± 9.30	20.03 ± 11.92						
Fractional Anisotropy	Left	0.444 ± 0.031	0.437 ± 0.033	0.01	0.919	4.66	0.041	0.80	0.379
	Right	0.421 ± 0.017	0.428 ± 0.028						
Apparent Diffusion Coefficient (x 10^{-3}mm^2/s)	Left	0.714 ± 0.021	0.719 ± 0.031	0.02	0.883	26.98	<0.001	0.21	0.652
	Right	0.689 ± 0.022	0.685 ± 0.026						

ADC, there were no significant group-by-hemisphere interactions, so t-tests were not used.

As shown above, in both groups, the CSA of the anterior thalamic peduncle, average FA value, and average ADC value were significantly higher in the left hemisphere than in the right. And the bipolar patient group had a significantly smaller CSA of the anterior thalamic peduncle than the control group for the left side, and the right side. For FA and ADC, there were no significant differences between patient and control groups for both sides.

4. Discussion

To our knowledge, this is the first study to assess the anterior thalamic peduncle via DTI in bipolar patients, though Houenou *et al.*[33] did use DTI for fiber tracking of the uncinate fasciculus (connecting the frontal lobe and the temporal lobe), and observed a significant increase in the number of reconstructed fibers in patients with euthymic bipolar disorder. However, this is the first DTI study that used, as tracking targets, specific nerve bundles that are involved in fronto-thalamic connectivity which governs prefrontal function. For this purpose, we performed fiber tracking of the anterior thalamic peduncle (a nerve fascicle that runs from the thalamus towards the frontal lobe by way of the anterior limb of the internal capsule) and created its tractographs using a tractography-based ROI technique (**Fig. 1**).

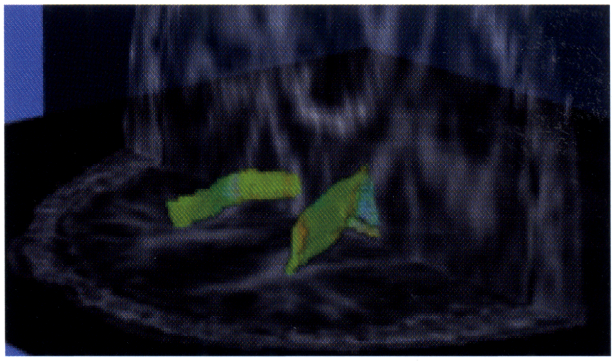

Fig.1 A tractograph of the anterior thalamic peduncle
This is a tractograph of the anterior thalamic peduncle of one participant from normal comparison group.

First, regarding the CSA of the anterior thalamic peduncle, this study showed that both right and left hemispheres are significantly smaller in patients with bipolar disorder than in the healthy controls. As mentioned before, Buchsbaum and his colleagues reported the reduction in the volumes of the white matter of the prefrontal cortex [24]. Moreover, McIntosh *et al.* [34] reported that the white matter density in the anterior limb of the internal capsule was lower in bipolar patients than in healthy controls. Anatomically, the anterior thalamic peduncle comprises a part of the anterior limb of the internal capsule. It is possible that white matter abnormalities observed by McIntosh *et al.* reflect a decrease in the CSA of the anterior thalamic peduncle, as we had observed. This reduction of CSA in both sides of the anterior thalamic peduncle may suggest that white matter abnormalities linked to bipolar disorder are bilateral in nature.

As for ADC and FA values, meanwhile, this study showed no significant differences between the patient group and the control group. Bipolar disorder is reported to show a rise in ADC values in the orbital frontal white matter [35] and a reduction of FA values in the prefrontal white matter [36, 37]. If we restrict the scope for comparison to the anterior limb of the internal capsule, however, we find that our results are in keeping with Haznedar *et al.* [24], reporting no inter-group differences in FA.

In our study, FA and ADC were significantly higher in the left anterior thalamic peduncle than the right in both the patient and healthy control groups. In their DTI study using the voxel-based morphometry (VBM) method, Park *et al.* reported the existence of left-right asymmetry in the FA of the healthy control group in various areas of brain (e.g. the anterior part of the corpus callosum, cingulum bundle, the optic radiation, the superior cerebellar peduncle, the anterior limb of the internal capsule, the anterior limb's prefrontal regions, the uncinate fasciculus, and the superior longitudinal fasciculus) [38]. The findings of our study did not contradict these findings. Moreover, in our present study, regarding the anterior thalamic peduncle, the patient group also showed the same type of left-right asymmetry as the control group showed.

Thus, the fact that prefrontal dysfunctions involving attention/processing speed, memory, and executive function are seen in bipolar disorder [39], despite their having no clear morphological abnormalities in the prefrontal region or the thalamus, suggests the involvement of a fronto-thalamic connectivity impairment in the pathology of bipolar disorder. The decreased CSA of the anterior thalamic peduncle seen in this study might provide possible indications that some neurodevelopmental abnormalities have developed bilaterally in the white matter fiber of the anterior thalamic peduncle. McIntosh *et al.* [40] report that if variations occur in Neuregulin 1 (NRG1), a gene that influences neuronal migration, axon guidance, and myelination, the anterior limb the of internal capsule shows reduced white matter intensity and reduced FA values. Although reduced FA values were not founded in this study or in the study by Buchsbaum and his

colleagues [24], these findings suggest the possible involvement, in the pathology of bipolar disorder, of bilatreral neurodevelopmental abnormalities that bring about a reduction in the white matter fiber of the anterior thalamic peduncle.

This study has several possible limitations. Patients with bipolar disorder who took part in this study were taking mood stabilizers and other psychotropics when their DTI were taken. The actions of the psychotropics thus may have influenced the results of this study. Recent studies have shown, however, that mood stabilizers have neuroprotective actions. Examples include one finding from a postmortem brain study by Bowley *et al.* [41] showing that, although the number of glial cells was not lower in bipolar patients who had been taking mood stabilizers, the number was lower in patients who did not use such drugs; another finding revealed that patients on lithium had a significantly large volume of the hippocampus on the left side [42]; and yet another report showed that, although the volume of the cingulated gyrus was not lower in bipolar patients on lithium, the volume of the left anterior cingulated gyrus seemed to be lower in patients not taking the drug [43]. Considering these findings as a whole, it is unlikely that mood stabilizers had triggered a reduction in white matter fiber of the anterior thalamic peduncle. However, these reports are not studies about white matter *per se*, so it remains unclear whether mood stabilizers have neuroprotective actions towards the white matter fiber or not. Moreover, if we consider that the average FA and ADC values of the patient group and the normal control group in both right and left hemispheres were practically the same, showing no significant differences, we can assume that FA and ADC are unaffected by psychotropics. Likewise, it may be appropriate, to a degree, to believe that the differences seen in CSA are not attributable to psychotropics, but to the disease *per se*.

On the other hand, some attention needs to be paid to the possibility that the patient group in this study did not represent the general population of bipolar patients, because of the small number of subjects, and the higher proportion of bipolar II patients than bipolar I patients, attributable to the limited capability of Kyorin University Hospital to treat and manage patients with severe manic, bipolar I disorder (*e.g.* absence of a quiet room). Finally, to conduct more definitive tracking, as for the conditions of the termination of fiber trajectories and the elimination of mal-reconstructed fibers, pursuits of optimal settings might be needed.

5. Conclusion

This study identified the presence of bilateral structural abnormalities of the white matter fiber of the anterior thalamic peduncle in bipolar disorder, which was congruent with the findings of Buchsbaum and his colleagues [24]. Our results suggested that impairment of fronto-thalamic connectivity, which resulted from the decreased CSA of the anterior thalamic peduncle, was involved in the prefrontal dysfunctions of the bipolar disorder.

Tractography-based ROI makes it possible to conduct fiber tracking of specific nerve bundles and to quantify diffusion anisotropy, suggesting the possibility of detecting even more minute structural abnormalities of the white matter fiber. Although further studies with more participants are needed, fiber tracking studies that target specific nerve bundles are a potentially useful means of further elucidating the pathology of bipolar disorder, and are anticipated to provide new possibilities for DTI studies.

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双極性障害における前視床脚の断面積減少：線維追跡法による研究

(Decreased Cross-Sectional Area of The Anterior Thalamic Peduncle In Bipolar Disorder: A Fiber Tracking Study)

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要旨：大脳白質の統合異常が双極性障害の病理に関与しているという仮説がある。前視床脚は視床と前頭葉をつなぐ神経線維束であり、双極性障害の認知障害に関連している可能性がある。本研究でわれわれは、11 名の双極性障害患者および 15 名の健常対照群から拡散テンソル画像を入手し、前視床脚の線維追跡を行うことでトラクトグラフィを作成した。前視床脚の断面積 (CSA)、拡散異方性 (FA)、みかけの拡散指数 (ADC) を計測し、患者群と健常群とを比較した。健常群と比べ、患者群では右および左の前視床脚において断面積が有意に小さかった。ADC と FA とに関しては、患者群と健常群とで有意さは認められなかった。両群共に、CSA、FA、ADC は右よりも左の前視床脚の方が有意に大きかった。これらの所見は、双極性障害における、視床と前頭葉との間の白質の統合の乱れを示唆している可能性がある。両側性の神経発達不全が、双極性障害の病理と関連しているかもしれない。

Keywords: anterior thalamic peduncle, bipolar disorder, diffusion tensor imaging, fiber tracking, white matter

概　要

1. 緒　言

1987 年 Dupont らにより、MRI の T2 強調像において双極性障害患者の皮質下に白質高信号がみられたという報告が行われて以降、白質高信号が双極性障害に特徴的な画像所見であるという臨床研究が相次いで報告された。それらは水内容の局所的変化を反映するものであると考えられたが、その臨床的意味については不明な点が多かった。

一方で、双極性障害においては、視床を含む皮質下の活性異常や、前頭葉の機能低下が指摘されている。しかし MRI を用いた形態学的研究では、視床に関しては患者群と対照群との間に形態的な変化を認められない。また前頭葉に関しては、患者群での体積減少を報告するものと、変化を認めないと報告するものとが折半しており、いまだに結論が出ていない。

これらの結果を考えると、視床と前頭葉とを結ぶ白質線維の結合に何らかの異常があるという仮説が産み出される。拡散テンソル画像をもちいて、白質の統合性について研究することが、その仮説を検証する手段となりうる。拡散テンソル画像は、生体内の水分子の拡散現象を非侵襲的に測定する方法である。白質では神経線維に沿った方向の拡散は速く、神経線維と直行する方向の拡散は遅いため、水分子の拡散現象を測定することにより、走行している神経線維の方向性を定量的、定性的に検出することが可能である。

Bachsbaum ら[24]は、双極スペクトラム群の前頭－視床－線条体の連絡網について調査し、健常群と比べ、双極性障害患者では前頭葉の白質体積は減少しているが、内包前脚の拡散異方性は変化していないことを報告した。しかしながら、この研究は region-of-interest (ROI) 法で行われている。ROI 法は、関心領域をどこに設定するかで、結果が大きく異なってしまう可能性がある。

われわれは、視床と皮質間の神経連絡を担い、視

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床から内包前脚を経て前頭葉へと向かう神経束である前視床脚を標的として白質の構造異常を検出するために神経線維追跡を行い、その tractgraphy を基に拡散異方性を定量する方法 tractography-based-ROI により解析を行った。

2. 方 法

本研究について書面による充分な説明を行った上で同意が得られた DSM-IV に基づく双極性障害患者 11 名と、年齢、性別を一致させた健常対照群 15 名を対象とした **(Table 1, 2)**。なお本研究は、杏林大学医学部医の倫理委員会の承認を得て行われている。拡散テンソル画像の撮影には Philips 社製の 1.5T Intera Achieva NovaDuel を使用し、前視床脚の線維追跡および拡散異方性の計測には著者である小林らの作成したプログラムを用いた。統計学的解析には SPSS for Windows 14.0J を用いて ANOVA を施行した。

3. 結 果

断面積に関して、患者群および健常群の間で有意差がみられた。半球間でも有意差がみられた。群－半球の相互作用は認められなかった。FA と ADC に関して、半球間で有意差がみられた。患者群と健常群との間では有意差がなく、群－半球の相互作用も認められなかった **(Table 3)**。

以上の通り、患者群、健常群のどちらにおいても、前視床脚の断面積、FA、ADC の各値は、右よりも左のほうが有意に高かった。そして患者群では、両側の前視床脚断面積が健常群より有意に小さかった。

4. 考 察

われわれの知る限り、これは双極性障害において拡散テンソル画像を用いて、前視床脚を評価した初めての研究であり、視床－前頭葉間の接続を担う特定の神経線維束を追跡した初めての研究でもある。そのためにわれわれは、前視床脚の線維追跡を行い、トラクトグラフィを作成した **(Fig. 1)**。

まずは双極性障害における断面積減少に関してである。Buchsbaum ら [24] は、前頭葉の白質の体積減少を報告している。加えて、McIntosh ら [34] は、双極性障害における内包前脚の白質密度の減少を報告している。解剖学的に、前視床脚は内包前脚の一部を構成している。McIntosh らによる内包前脚の白質密度の減少は、われわれが観察した前視床脚の断面積減少と関連しているかもしれない。この両側断面積減少という所見は、双極性障害における白質異常が両側性である可能性を示唆しているかもしれない。

FA と ADC とに関しては、われわれの研究では、患者群と健常群との間で有意差を認めなかった。双極性障害において、前頭前野の FA 低下を示唆する報告 [36,37] がいくつかあるが、内包前脚に限れば、Haznedar [24] らが報告しているように、FA 低下は認められておらず、われわれの所見と矛盾しない。FA や ADC の左右差に関しては、Park ら [38] による報告があり、これも特に矛盾しないものと考えられた。

双極性障害では前頭前野の機能に障害が出るにも関わらず、形態学的には、前頭葉や視床に異常所見が指摘されないという事実からは、視床と前頭葉との間の結合の障害が双極性障害の病因となっている可能性が示唆される。McIntosh ら [42] は、ミエリン化などに関係する Neuregulin 1 遺伝子に異常があると、内包前脚の白質信号が減少することを報告した。これらの所見からは、前視床脚の白質線維の減少をもたらすような両側性の神経発達異常が双極性障害の病理である可能性が示された。

(Tables 1-3, Fig. 1 英文参照)