Figure 3. Effects of the DISC1 protein on the ERK and Akt signaling in cortical neurons. (**A**) Suppression of phosphorylation of ERK and Akt in DISC1-siRNA-transfected cultures. Cortical cultures after DIV4 were treated with siRNA for DISC1 (si-DISC1; 100 nM) or control (scramble; 100 nM) for 72 h. Cortical cultures were harvested at DIV7 for western blotting for pERK1/2, ERK1/2, pAkt, Akt, DISC1 or TUJ1. The immunoblots shown are representative of four independent experiments (a). Quantification of the immunoreactivity of pERK1/2 (b), pAkt (c) or DISC1 (d). Quantitative data represent the mean ± SD ($n = 4$). ***$P < 0.001$ versus scramble. (**B**) (a) Double staining with GFP (green) signal and immunostaining signal by anti-MAP2 (red, a neuronal marker) antibody after sindbis virus-mediated gene transfer. Representative control (GFP only)-infected cortical cultures were shown. (b) GFP and DISC1 signal after sDISC1 (*upper*) or cDISC1 (*lower*) gene transfer, respectively. DISC1 localization was detected as a red signal. Virus infection was performed at DIV4 and infected cultures were fixed at DIV6 for immunostaining. Bar = 50 μm. (**C**) Differential activation of ERK and Akt between sDISC1 and cDSIC1. Samples for blotting pERK1/2, ERK1/2, pAkt, Akt, GFP, DISC1 or TUJ1 were prepared 24 h (DIV5) after viral infection at DIV 4 (a). The quantification of pERK1/2 (b) or pAkt (c) levels after overexpression of sDISC1 or cDISC1 was shown. The immunoblots shown are representative of four independent experiments. Quantitative data represent the mean ± SD ($n = 4$). **$P < 0.01$, *$P < 0.05$ versus control, ## $P < 0.001$ versus sDISC1. (**D**) (a) Recovery of the activation of ERK1/2 and Akt after sDISC1 and cDISC overexpressing in DISC1 knockdown cultures. To downregulate endogenous DISC1, si-DISC1 was applied at DIV4 or DIV5 cultures. Sindbis virus-infection for sDISC1 or cDISC1 overexpression was performed 48 h after the si-DISC1 treatment. Samples for blotting for pERK1/2, ERK1/2, pAkt, Akt, GFP, DISC1 or TUJ1 were prepared 48 h after viral infection. The immunoblot images are representative of five independent experiments. (b) The quantification of pERK1/2 for each experimental condition was shown. Quantitative data represent the mean ± SD ($n = 5$). **$P < 0.01$, *$P < 0.05$ versus si-DISC1.

We demonstrated that healthy subjects with the risk allele carriers for MDD (cys-DISC1) had relatively reduced the gray matter volumes in cingulate cortex, relatively expanded CSF space and reduced the FA values in the prefrontal white matter. This pattern of changes on magnetic resonance imaging (MRI) scanning, specifically the gray matter volume deficits in the ACC, expanded the CSF and reduced the FA values in prefrontal cortex, has been repeatedly reported in the studies of patients with schizophrenia and MDD (22,27–29). Several studies demonstrated a decreased volume in the ACC in patients with MDD in remission, MDD with a family history or in early onset depression (30–33) and abnormalities of cortical neuronal organization in postmortem brain of MDD have been reported in the ACC (34). It has been reported that relatively higher FA is associated with remission of MDD, following treatment with drugs or electroconvulsive therapy; however, reduced prefrontal FA has not been reported consistently in MDD (29,35–37). These various findings suggest that decreased gray matter volume and FA in the frontal area might be associated with the increased risk for MDD. Previous studies found that the risk haplotype of the DISC1 gene affected cortical gray matter and that Ser704Cys SNP had an impact on the hippocampal structure and function (9,11); however, we did not observe either effects of SNPs associated with schizophrenia in our sample on cortical gray matter or effects of Ser704Cys SNP on hippocampal volume. Moreover, in our study of the effect of Ser/Cys genotype on brain imaging derived phenotypes and clinical association, it is the cys allele that is relatively deleterious, whereas in an earlier study, it was the ser allele (9). These inconsistencies may relate to sample differences, methodological differences, and also to possible genetic and allelic heterogeneity.

We found robust effects of DISC1 on ERK and Akt signaling and evidence that the cDISC1 (the risk allele for MDD) might exert a weaker effect on the ERK activation than sDISC1. The involvement of ERK in the therapeutic mechanisms of mood disorder has been proposed (38,39). It has been shown that ERK can phosphorylate PDE4 and alter its activity (40,41) and that PDE inhibitors might have antidepressant efficacy (24). Taken together, the regulation of ERK signaling by DISC1 may contribute, at least in part, to the mechanisms of the risk for MDD. Structural imaging studies have demonstrated reduced gray matter volumes and white matter abnormality in several brain areas of patients with mood disorders relative to healthy controls, and postmortem morphometric brain studies also demonstrated cellular atrophy and/or loss (24). As the ERK kinase signaling is implicated in cytoskeletal remodeling, neurite outgrowth and cell survival (24) and decreased expression of ERK was observed in the postmortem brain of depressive patients (42), impaired ERK signaling could be related to the structural abnormality in major depression.

In conclusion, we have found evidence for association between genetic variation of DISC1 and MDD, brain morphology and ERK signaling pathway. Our data suggest that Ser704Cys might be a functional variant that impacts on neural mechanisms implicated in the biology of major depression.

MATERIALS AND METHODS

Subjects

Subjects for the clinical association study were recruited at Fujita Health University School of Medicine, Showa University School of Medicine and National Center of Neurology and Psychiatry, Japan. They were 373 patients with MDD [147 males and 226 females with mean age of 54.0 years (SD 16.0); mean age of onset of 46.5 years (SD 15.3)], 658 patients with schizophrenia [340 males and 318 females with mean age of 43.6 years (SD 14.6); mean age of onset of 24.2 years (SD 8.6)] and 717 healthy comparison subjects [351 males and 366 females with mean age of 41.3 years (SD 16.9)]. All the subjects were Japanese. Consensus diagnosis was made for each patient by at least two psychiatrists, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV Criteria). Control subjects were healthy volunteers who had no current or past contact to psychiatric services.

One hundred and eight healthy Japanese (biologically unrelated) for MR experiments were recruited at the National Center of Neurology and Psychiatry and screened by a questionnaire on medical history and excluded if they had neurological, psychiatric or medical conditions that could potentially affect the central nervous system, such as substance abuse or dependence, atypical headache, head trauma with loss of consciousness, asymptomatic or symptomatic cerebral infarction detected by the T2-weighted MRI, hypertension, chronic lung disease, kidney disease, chronic hepatic disease, cancer or diabetes mellitus. Detail demographics of subjects in genotypes of SNP1, SNP7, SNP9 and SNP12 (Ser704Cys) were noted in Supplementary Material. After description of the study, written informed consent was obtained from every subject. The study protocol was approved by institutional Ethics Committees.

Genetic analysis

Venous blood was drawn from subjects and genomic DNA was extracted from the whole blood according to the standard procedures. Thirteen SNPs were genotyped using the TaqMan 5′-exonuclease allelic discrimination assay as described previously (43,44). Primers and probes for detection of the SNPs are available upon request. Statistical analysis of association studies was performed using SNPAlyse (DYNACOM, Yokohama, Japan). Allele distributions between patients and controls were analyzed by the χ^2 test for independence. The measure of LD, denoted as D' and r^2, was calculated from the haplotype frequency using the expectation–maximization algorithm. Case–control haplotype analysis was performed by the permutation method to obtain the empirical significance (45). The global P-values represent the overall significance using the χ^2 test when the observed versus expected frequencies of all the haplotypes are considered together. The individual haplotypes were tested for association by grouping all others together and applying the χ^2-test with 1 df. P-values were calculated on the basis of 10 000 replications. All P-values reported are two tailed. Statistical significance was defined at $P < 0.05$.

Neuroimaging analysis

Brain MR procedure is described in Supplementary Material. The basic principle of TBM is to analyze the local deformations of an image and to infer local differences in the brain structure. The method was described in detail previously (46) (Supplementary Material). Diffusion tensor imaging (DTI) analysis was performed using FA maps by a voxel-by-voxel analysis (Supplementary Material). The statistical parametric maps of Jacobian determinants and FA values were analyzed using statistical parametric mapping (SPM) 2, which implements a 'general linear model'. To test hypotheses about regional population effects, data were analyzed by a two-sample t-test without global normalization. We used $P < 0.001$ without a correction for multiple comparisons to avoid type-II error to explore whole brain and then applied small-volume correction ($P < 0.01$) to each cluster. Since there has been no a priori hypothesis for FA changes associated with DISC1 polymorphism, we applied conservative statistical threshold ($P < 0.001$) for the analysis of FA values. The resulting sets of t-values constituted the statistical parametric maps {SPM (t)}.

Molecular biology

Primary cultures were prepared from the cerebral cortex of postnatal 2-day-old rats (Wister ST; SLC, Shizuoka, Japan) as reported previously (47,48).

The siRNA transfection was performed as reported previously (49). We used 21 nt siRNA duplexes with two nucleotides of the rat DISC1 mRNA coding region (113–131, GACCAGGCTACATGAGAAG, NM_175596). Sense (GAC CAGGCUACAUGAGAAGtt) and antisense (CUUCUCAU GUAGCCUGGUCtc) strands were chemically synthesized by Ambion Ltd (Cambridge, UK). The siRNA (GCGCGC UUUGUAGGAUUCG) named ScrambleII from Dharmacon Research Inc. was used as a scramble control. The plasmid for viral construction of the DISC1 gene was derived from pSinRep5 (Invitrogen, USA) and had two subgenomic promoters followed by a multiple cloning site for an arbitrary gene insertion and an enhanced GFP open-reading frame, thus the virus can produce both arbitrary protein and enhanced GFP independently in the infected cell (50). The control virus produces GFP only, whereas DISC1 virus produces both DISC1 and GFP independently. Detail procedure for viral construction is in Supplementary Material.

Immunocytochemistry was performed, as described previously (51). We used anti-MAP2 (1:1000; Sigma) or anti-DISC1 (1:100) (17) antibodies as a primary antibody, respectively. Alexa Fluor (1:1000, Molecular Probes) was applied as a secondary antibody. Fluorescent images were observed by an inverted microscope (Axiovert 200, ZEISS) with a CCD (cool SNAPfx, ZEISS).

Immunoblotting was carried out as described previously (47). Primary antibodies for immunoblotting were used at the following dilutions: anti-Akt (1:1000, Cell Signaling), anti-phospho-Akt (1:1000, Cell Signaling), anti-ERK (1:1000, Cell Signaling), anti-phospho-ERK (1:1000, Cell Signaling), anti-TUJ1 (1:5000, Berkeley antibody company), anti-GFP (1:1000, Medical & Biological Laboratories) and anti-DISC1 antibodies (1:1000) (17). To quantify the amount of proteins after immunoblotting, we measured the density of immunoblots with an image-analysis software (Science Lab 98 Image Gauge; Fuji Photo Film Co. Ltd, Tokyo, Japan). The level of protein expression was indicated as a ratio that was normalized to control the condition (none, sole GFP-infected, or scramble-transfection, respectively) in each experiment. Statistical analysis was performed with unpaired t-test or ANOVA, followed by the Tukey *post hoc* comparisons when applicable.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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ヒトの大脳皮質基底核連絡線維

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ヒトの大脳皮質基底核連絡線維

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はじめに

局所脳機能は、外因的特性(線維連絡パターン)と内因的特性(細胞構築、局所神経回路等)に規定される[1]。大脳深部灰白質のうち大脳皮質と同じく終脳から発生した大脳基底核は、運動、認知、感情、報酬、学習、言語など様々な脳機能に関連する重要な脳部位である。大脳基底核の中で入力中継地である線条体は被殻と尾状核に分かれるが、発生学的には同じ構造物で、細胞構築も比較的均一で組織化学染色でも明確な線条体内の境界は認められない。そのため、古くからサル脳において線維連絡性に基づいた線条体内の分節化が試みられてきた。ヒト脳の線維連絡性はこれらサル実験の結果から外挿されるのみで、両種間の違いは無視

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されてきた。本稿では、大脳皮質・基底核(特に線条体)間の連絡性について近年技術の進歩のめざましい非侵襲的画像法による試みを紹介する。

サル脳からの推定

サル脳での大脳皮質基底核間の線維連絡は、放射能標識アミノ酸や西洋ワサビ過酸化酵素など神経追跡トレーサーを用いた検討から、大脳皮質下行線維が線条体内の最も近い場所に投射する proximity rule[2]や、長軸方向に延びるように投射する longitudinal pattern[3]、大脳皮質-大脳基底核-視床-大脳皮質からなる parallel loop[4]などが提唱された(図1)。また Parent らは線条体を大脳皮質との線維連絡性により limbic, associative, sensorimotor striatum の3領域に分けた[5]。近年、サル脳で大脳皮質から視床への逆
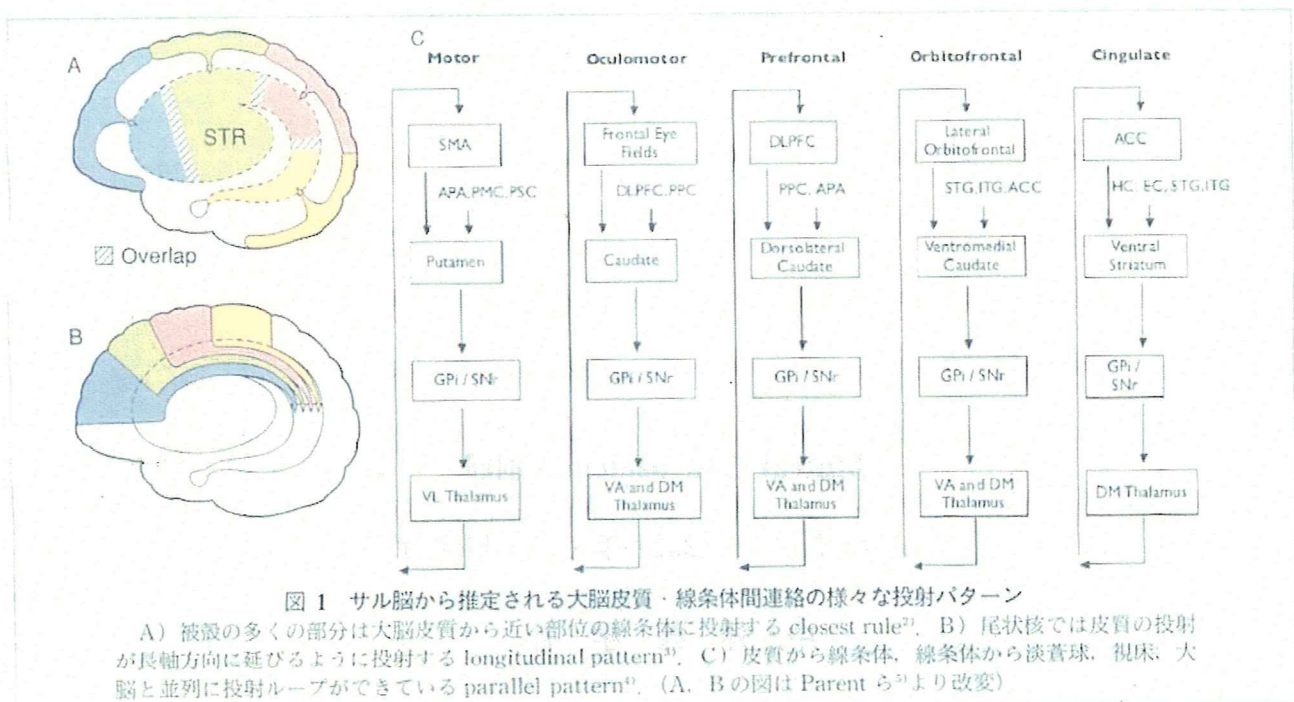

図1 サル脳から推定される大脳皮質・線条体間連絡の様々な投射パターン
A) 被殻の多くの部分は大脳皮質から近い部位の線条体に投射する closest rule[2]。B) 尾状核では皮質の投射が長軸方向に延びるように投射する longitudinal pattern[3]。C) 皮質から線条体、線条体から淡蒼球、視床、大脳と並列に投射ループができている parallel pattern[4]。(A、Bの図は Parent ら[5]より改変)

行性線維や，視床から線条体への逆行性線維が発見され[6]，大脳皮質・基底核回路は，従来考えられたよりも複雑な回路網を形成していることもわかってきた．

ヒト脳での解明

ヒト脳の大脳皮質と基底核の連絡性は，近年の非侵襲的画像法の進歩により徐々に明らかにされようとしている．直接解剖学的線維連絡の評価ができない中で，脳機能評価法による「機能的連絡性」という概念が生まれた．これは脳の神経活動を捉える手法〔脳波，脳磁図，ポジトロンエミッショントモグラフィー(PET)や機能的磁気共鳴画像法(fMRI)法〕の分野で生まれたもので，脳の離れた部位で得られる脳波形のコヒーレンスや画像信号の相関関係(functional connectivity)を含む．

特にPETやfMRIは大脳皮質だけでなく深部灰白質の活動を評価できるので，皮質・線条体間の機能的連絡性を調べられる．Postumaら[7]は機能画像研究のメタアナリシスにより，さまざまな課題遂行時の脳機能画像(PETまたはfMRI)の結果を横断的に検討し大脳皮質と線条体の各部位の共活動を観察した(図2)．背側・吻側の線条体は前
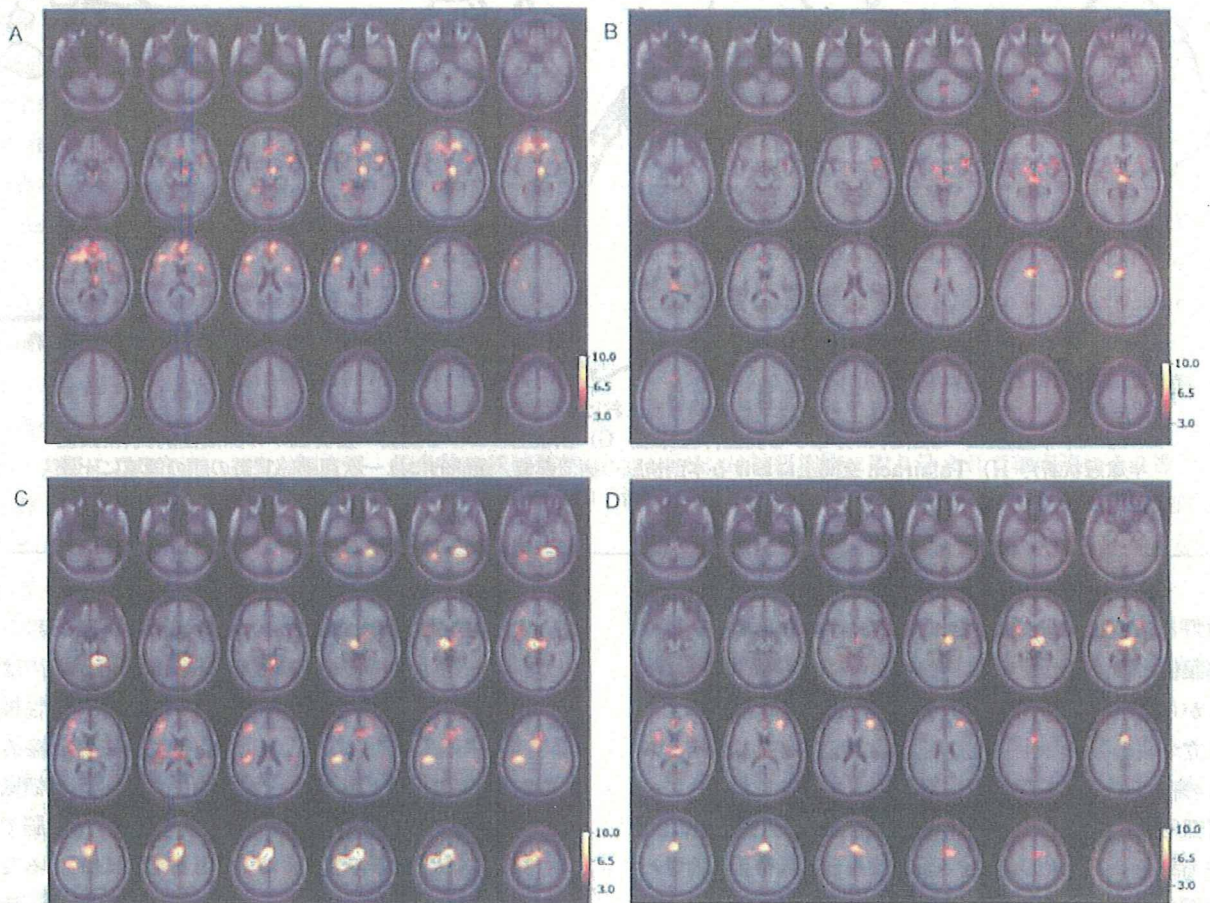

図2 ヒト脳の皮質・線条体間の機能的連絡性
A) 左尾状核，B) 右尾状核，C) 左被殻，D) 右被殻の活動と，統計学的に有意に相関した脳部位．1992〜2001年に出版された基底核の活動を認めた126のPET/fMRI研究結果をまとめたもの．カラーバーはICBM 152ヒト標準脳上の統計値(t値)を示す．尾状核の活動は前頭前野背側・腹側と相関した(特に左側，A)．被殻の活動は運動野，補足運動野，小脳皮質と相関した(特に左側，C)．(Postumaら[7]より改変)
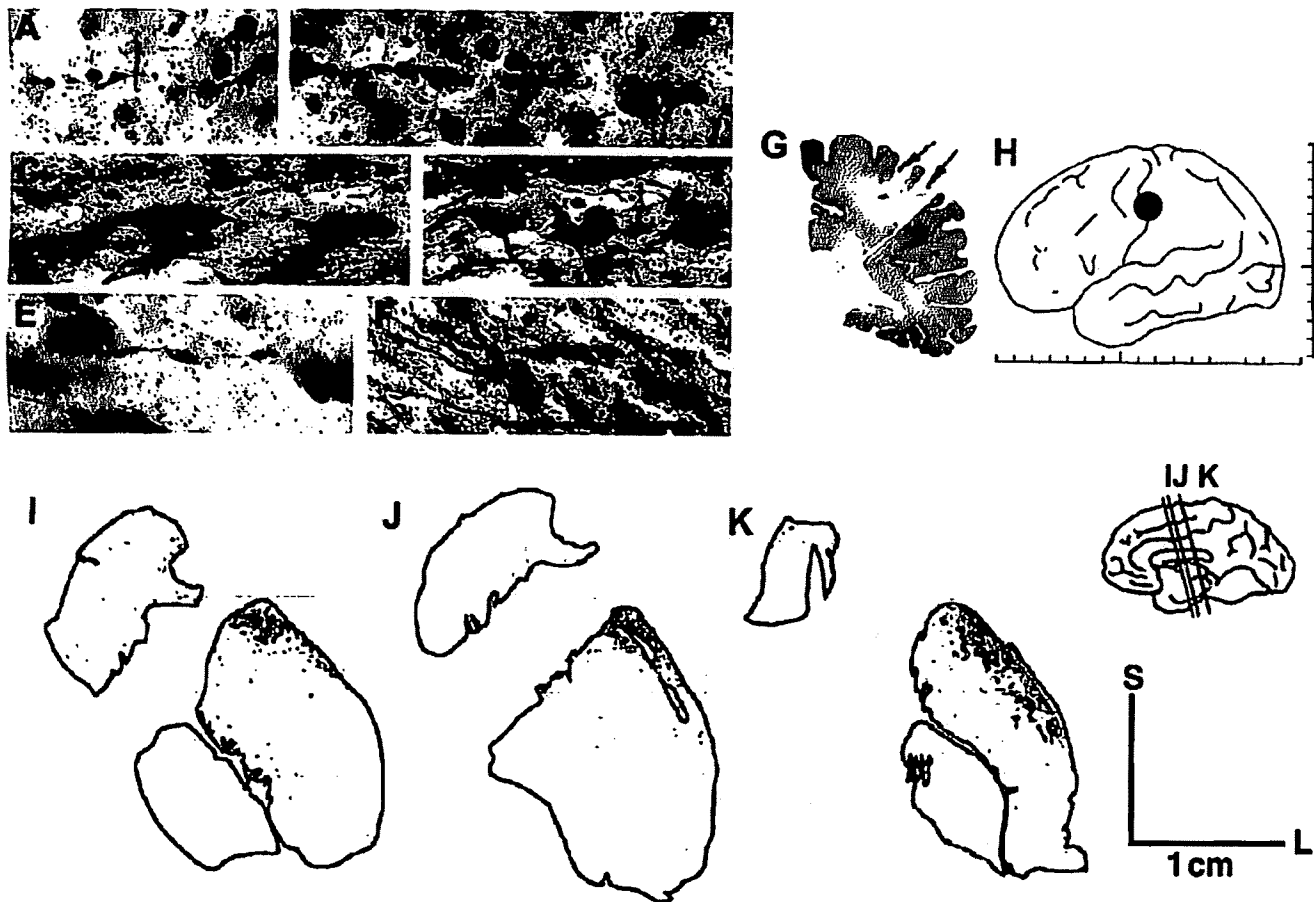
図3 ヒト剖検脳における皮質・線条体線維
A〜F）大脳皮質〜線条体に分布する変性神経線維. G）剖検脳における皮質・皮質直下の陳旧性病変（左大脳半球冠状断）. H）Talairach 空間上における本剖検脳の病変部位. 機能的には一次運動感覚野の顔の領域に一致した. I〜K）線条体内で変性神経線維が分布した場所.（Wiesendanger ら[10]より改変）

頭前野と，被殻後部は運動野や前運動野と，腹側線条体は中脳腹側との共活動が多くみられた.

しかし機能的連絡性は，"既知の"解剖学的連絡性の上に成り立つ概念である. また相関関係の強度は別の脳内システムの作用により変化すると考えられる（例えばシナプスの可塑的変化を介して）. そこで（サル脳で得た）解剖学的連絡性を制約モデルとして機能画像で得た機能的連絡性をパス解析することで被験者の状態等による違いをみる方法も提唱された[8]. 実際 Toni ら[9]は fMRI を用い，視運動課題を学習する際に前頭葉皮質・線条体間の神経活動の共活動に変化が生じることを観察し，特定の皮質・線条体回路の強化により学習が構築されることを示した.

ヒトの解剖学的な大脳皮質・線条体の線維連絡については唯一剖検脳での研究がある. Wiesendanger ら[10]は生前に大脳皮質に病変を来した脳の切片において，変性神経線維を染色する方法（Nauta 法）により大脳皮質・線条体の線維連絡を調べた（図3）. 一次運動感覚野の顔の領域に一致すると考えられる部分に陳旧性病変を持つ剖検脳で，変性神経線維が被殻後背側部に集中して位置していることを確認した. これはサルで調べられた結果ともよく一致している. しかしこの観察法の検出感度は不明で多数の脳や部位で検討できない.

Diffusion-based tractography

近年, 拡散テンソル MRI(DTI)法の撮像・解析技術の進歩により, ヒトの脳でも脳内の巨視的線維連絡性の評価 (diffusion-based tractography)が可能になりつつある. この方法はそもそも脳内の水分子の拡散運動(diffusion)の特異性に基づいている. すでに 1980 年代から脳内の水分子の拡散運動が空間的に均等(等方性 isotropic)ではないという特殊な物理的性質をもっていることが知られていた[*1]. この水分子の拡散移動の空間的特徴を, motion probing gradient(MPG)[*2]という傾斜磁場を均等に多方向(最低 6 方向)で用いることで, 拡散運動による移動度を数学的概念である tensor として表現するのが DTI 法である[12]. すなわち脳内のある一点に注目すると, その部分の水分子が全く自由に拡散する(等方性)のであれば, 原点からの水分子の相対的移動度は球になり, 方向依存性に拡散が制限される場合(異方性 anisotropic)には楕円体になる[*3]. この楕円体を tensor で表現すると, その最も長い軸方向(第一固有ベクトル principal eigenvector)は同画素内で支配的に存在する神経線維方向に一致すると考えられる(図4 A). これを隣りの画素同士たどっていくのが神経線維追跡法(diffusion-based tractography, 図4 B)で, この開発に日本人研究者の Johns Hopkins 大学の森 進教授が大きく貢献した[13]. 実際にこの方法により大脳皮質・線条体の線維連絡の追跡も行われた[14](図4 C).

しかし, diffusion-based tractography のデータ収集・解析法は現在も発展段階で精度も十分に検討されていない. 精度の高い拡散移動度の推定のために, MPG の角度解像度の高い画像や空間解像の高い画像撮像法の開発が進ん

でいる. 解析に, 非線形性を想定した一般 tensor モデルや, 確率的手法の導入によって追跡能を向上させ定量的に評価する手法等が開発されている. Behrens らは, 各画素における各方向への拡散移動の確率分布(pdf)を, ベイズの定理およびブートストラップ法というサンプリング法によって評価しそれに基づいて確率的に線維連絡を評価することで定量的で感度の高い方法(diffusion-based probabilistic tractography, DBPT)を提唱した[15]. 実際にこの方法によると大脳皮質との連絡性に基づいたヒト視床の分節化が可能で, 剖検脳から推定された視床内亜核にほぼ一致した[16].

著者らは DBPT を用いて正常人の皮質・線条体線維を解析した. 顔領域に一致する運動感覚野からの線維連絡性は被殻背外側部に分布した(図5). この結果は剖検脳で示された結果(図3)とよく一致しており, Parent ら[5]が皮質線維連絡性に基づいて線条体を分類した3分画のうちの一つ sensorimotor striatum の一部にも相当する.

さらに DBPT 法がどれほどの特異性・感度かみるため, サルの大脳皮質前頭葉の Brodmann 9 野(BA 9)からの DBPT による線維連絡性を, マンガン(Mn)を用いた神経線維追跡法と比較した[17]. BA 9 からの probabilistic tractography を行い, 同部位に Mn 溶液を注入することで, 両 tractography で尾状核, 被殻, 視床内側部, 中脳腹側, 脳梁など線維連絡性がほぼ同じ部位に分布した(図6 A). マンガンは神経細胞に取り込まれて軸索流により遠位に運ばれる前向性トレーサーなので[18], DBPT 法が比較的高い感度と特異性をもって神経線維を追跡できることを示唆する.

また線条体の中でも, ほぼ前交連より前, 腹側に位置する腹側線条体は線条体の中でも辺縁系との線維連絡性を強くもっていることがサル脳での研究から知られている[19]. ヒト脳とサル脳でこの部位から神経線維追跡を調べたところ, 両種とも前頭極, 前頭葉内側, 前頭葉腹側, 側頭葉に投射しているのが観察され(図6 B), サルのトレーサーでの実験結果にも一致した[17]. また前頭葉皮質を大きく5領域に分けてそれら各皮質領域のいずれかの最大線維連絡性を調べると, ヒト・サル脳ともに被殻において各皮質領域の線維が topographical に分布し closest rule に近いパターンを示すことが分かった(図6 C)[17]. 今後, サルにおけるトレーサーによる神経線維連絡の解明と同時にサル・ヒ

[*1]なぜ神経系で拡散が等方性でない(=異方性 anisotropic と呼ぶ)のか, 未だ完全にはわかってないが, 動物実験から, ①神経軸索内の長軸方向の巨大タンパク構造物や軸索流によるものでないこと, ② 無髄神経・有髄神経ともに異方性が高いこと, が示され, 主に軸索膜, 次に髄鞘膜が水分子の拡散運動を制限し異方性の原因となっていると考えられる(総説[11]参照).

[*2]1965 年に Stejskal & Tanner が開発した拡散を強調するための傾斜磁場. その後 1986 年に LeBihan らが医学領域への応用性を紹介し医学研究が進んだ. 特に急性期脳梗塞で強い拡散の変化が生じることが発見され EPI 法と組み合わせて高速撮像が可能となったことで臨床用 MRI 装置に導入が進んだ.

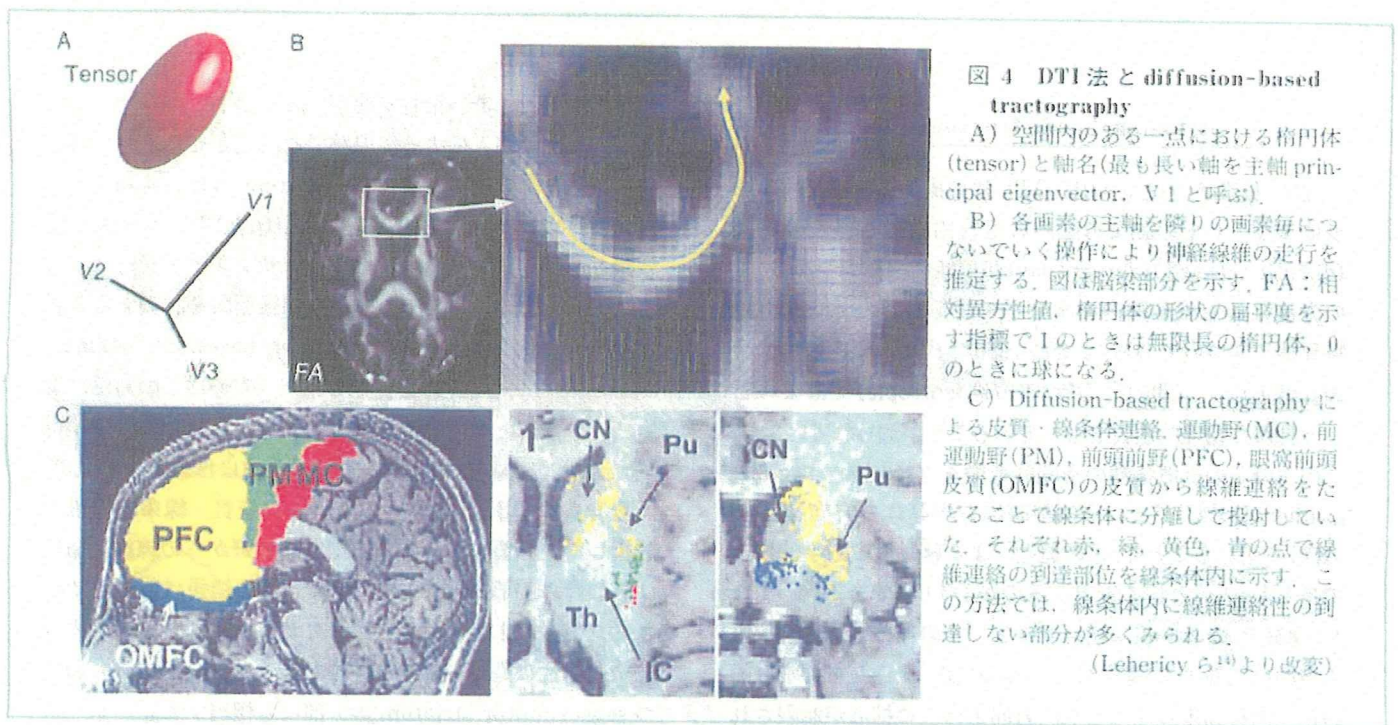[*3]この tensor model は非常に単純なモデルで, 拡散の均一性と線形性を仮定しているために単純な形状(楕円体)になる.

図4 DTI法とdiffusion-based tractography

A）空間内のある一点における楕円体(tensor)と軸名(最も長い軸を主軸principal eigenvector, V1と呼ぶ).

B）各画素の主軸を隣りの画素毎につないでいく操作により神経線維の走行を推定する. 図は脳梁部分を示す. FA：相対異方性値. 楕円体の形状の扁平度を示す指標でIのときは無限長の楕円体, 0のときに球になる.

C）Diffusion-based tractographyによる皮質・線条体連絡, 運動野(MC), 前運動野(PM), 前頭前野(PFC), 眼窩前頭皮質(OMFC)の皮質から線維連絡をたどることで線条体に分離して投射していた. それぞれ赤, 緑, 黄色, 青の点で線維連絡の到達部位を線条体内に示す. この方法では, 線条体内に線維連絡性の到達しない部分が多くみられる.
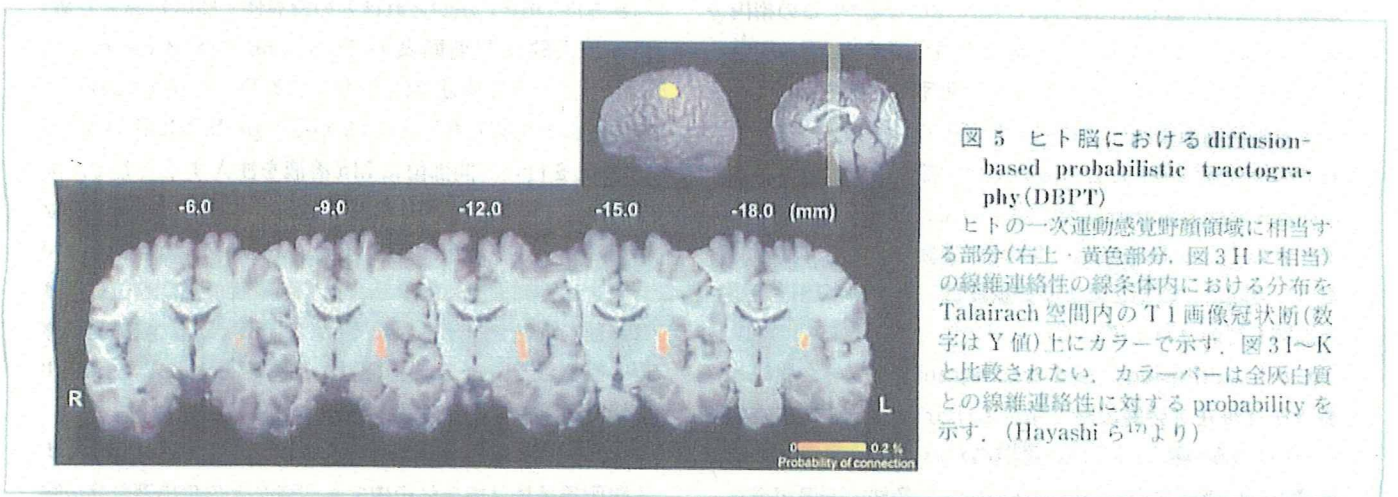(Lehericyら[19]より改変)

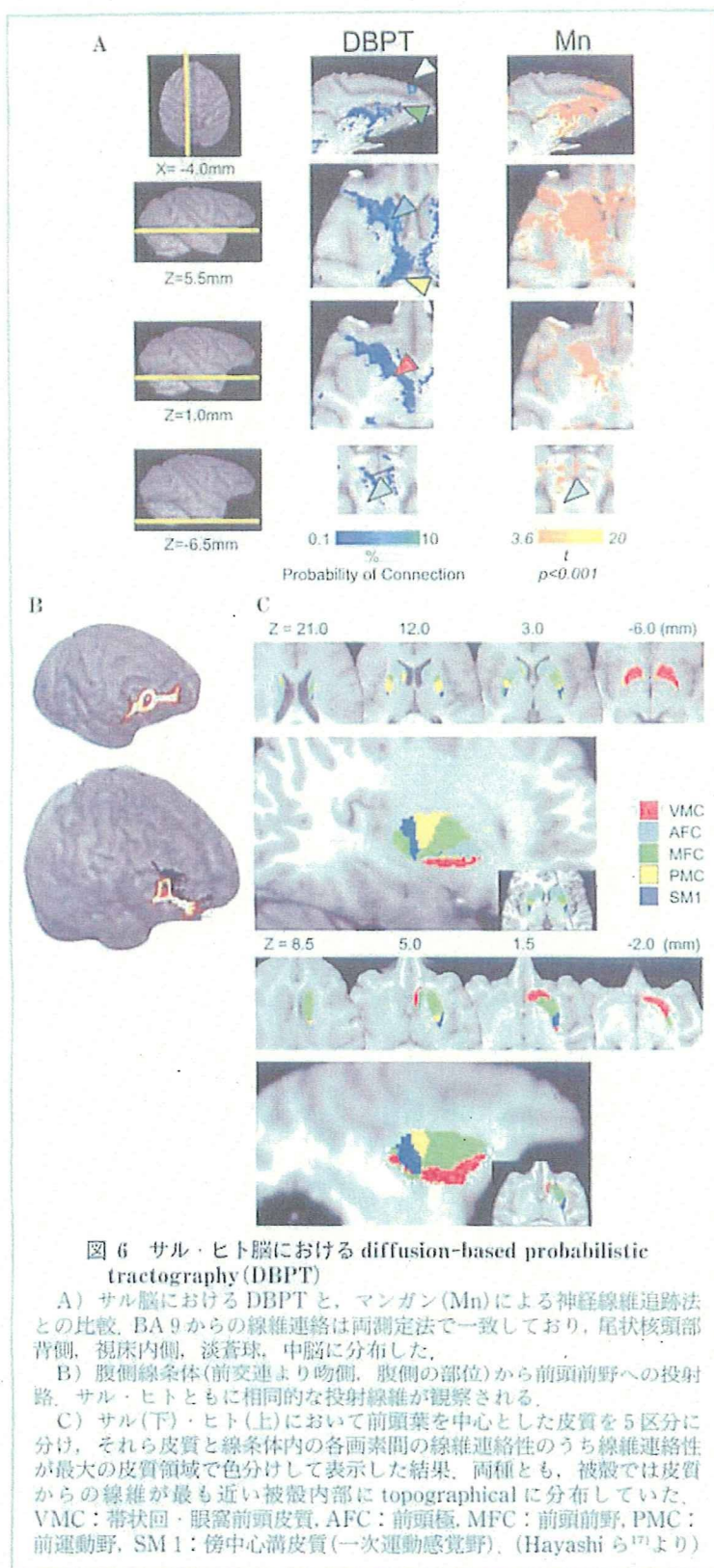図5 ヒト脳におけるdiffusion-based probabilistic tractography(DBPT)

ヒトの一次運動感覚野顔領域に相当する部分(右上・黄色部分, 図3Hに相当)の線維連絡性の線条体内における分布をTalairach空間内のT1画像冠状断(数字はY値)上にカラーで示す. 図3I〜Kと比較されたい. カラーバーは全灰白質との線維連絡性に対するprobabilityを示す. (Hayashiら[17]より)

トの両種でのDBPTによる詳細な解析が期待される.

今後の展開

ヒト脳の線維連絡性の評価は長らくサル脳からの推定か剖検脳による評価しかできない時代が続いた. DTI法や神経追跡法の更なる撮像・解析技術進歩によりヒトの解剖学的線維連絡性が明らかにされると期待されるが, 今後, 撮像技術の更なる改良に加え本法の精度評価も必要である. 特に「線維の連続性」や「線維の方向性(神経細胞→軸索末端または軸索末端→神経細胞)」の情報は本法では捉えられずトレーサー法で補う必要もある. 画像の高分解能化・高SN比, MPGの高角度分解能だけでなく, 静磁場不均一性やMPGのうず電流による画像歪みの対策等, 細かい技術の集積も重要である. 今後, ヒトの大脳皮質・大脳基底核の線維連絡性が明らかにされ基底核疾患の病態が解明されることを期待したい.

図6 サル・ヒト脳における diffusion-based probabilistic tractography（DBPT）

A）サル脳における DBPT と，マンガン（Mn）による神経線維追跡法との比較．BA 9 からの線維連絡は両測定法で一致しており，尾状核頭部背側，視床内側，淡蒼球，中脳に分布した．

B）腹側線条体（前交連より吻側，腹側の部位）から前頭前野への投射路．サル・ヒトともに相同的な投射線維が観察される．

C）サル（下）・ヒト（上）において前頭葉を中心とした皮質を5区分に分け，それら皮質と線条体内の各画素間の線維連絡性のうち線維連絡性が最大の皮質領域で色分けして表示した結果．両種とも，被殻では皮質からの線維が最も近い被殻内部に topographical に分布していた．VMC：帯状回・眼窩前頭皮質，AFC：前頭極，MFC：前頭前野，PMC：前運動野，SM 1：傍中心溝皮質（一次運動感覚野）．（Hayashi ら[17]より）

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