物質依存の神経化学

依存性薬物の中でメタンフェタミンやコカインなどはおもに中枢神経系を興奮させることから中枢神経刺激薬とよばれる．オピオイド類の麻薬であるヘロインはおもに抑制効果を示す．薬事法上は麻薬に分類されるフェンシクリジン（phencyclidine: PCP）はおもに幻覚を引き起こし，大麻は刺激・抑制に区分されにくい効果を示す．このように依存性薬物は摂取時の自覚効果から，刺激・覚醒効果が強い興奮系と鎮静・酩酊効果が強い抑制系に大別される．

依存性薬物の標的分子が遺伝子クローニングを用いた分子薬理学的手法により同定された．コカインやメタンフェタミンなどの中枢神経刺激薬はモノアミントランスポーター[1]，モルヒネやヘロインなどの麻薬はオピオイド受容体[2]，幻覚剤であるフェンシクリジンはグルタミン酸受容体，大麻はカンナビノイド受容体を標的分子とすることが明らかとなった[3]．

本項では薬物依存の基盤となるメカニズムとしての報酬系について概括し，おもに中枢神経刺激薬の標的分子が果たす役割について遺伝子改変マウスなどの分子遺伝学的手法を用いて得

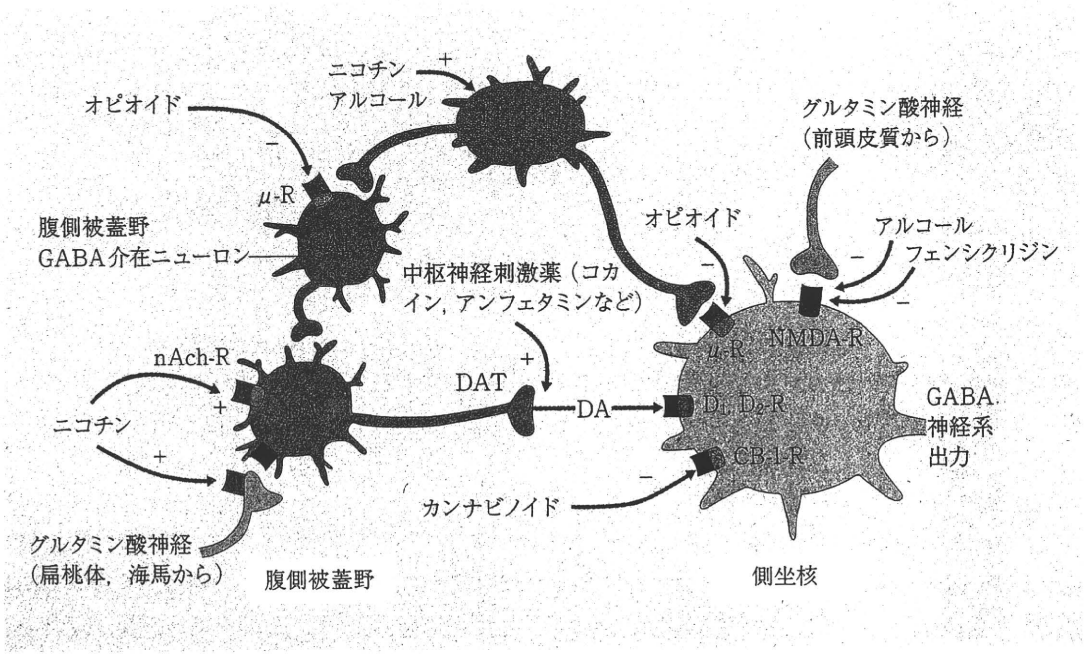

図1　依存性薬物の標的分子

μ-R（μ受容体），DA（ドパミン），DR（ドパミン受容体），DAT（ドパミントランスポーター），nAch-R（ニコチン性アセチルコリン受容体），NMDA-R（NMDA受容体），CB-1-R（カンナビノイド受容体）．
依存性薬物が共通に作用する部位として腹側被蓋野のドパミン神経細胞から，辺縁系ことに側坐核に投射する神経回路が担っている．

（Nestler EJ, 2005[8] より改変）

られた知見を紹介する．さらに薬物依存患者のゲノム遺伝子多型の解析により依存性薬物の標的分子に加えて，薬物依存の病態に関与する新たな分子についての報告も紹介する．

報酬系と薬物依存

中枢神経刺激薬やオピオイドなどの依存性薬物は，きわめて強い快情動を起こすことから，強い報酬効果を持つ[4]．この報酬効果は，依存性薬物がきわめて強い快情動を引き起こし，脳内に強固な神経伝達の可塑性の変化を起こしているものと考えられる．報酬効果に関与する神経伝達系は，ドパミン系が大きな役割を担うと考えられてきた[3,5]．ドパミン系の中でも腹側被蓋野（ventral tegmental area: VTA）から側坐核に投射する中脳辺縁系ドパミン経路の破壊は中枢神経刺激薬の報酬を著しく減少させることから，依存に重要な役割を果たしていることを示している[6]．

側坐核には，モルヒネやヘロインなどの麻薬のオピオイド受容体が存在することから，依存性薬物の報酬効果にはドパミン系に加えてオピオイド系も重要である[2]．オピオイド受容体以外にも依存性薬物の標的分子の受容体は側坐核や腹側被蓋野に投射する神経細胞上に多数，存在する．このように報酬系に関与する神経系は，単一ではなく複数の異なる系が関係すると考えられるが，依存性薬物が共通に作用する部位として腹側被蓋野のドパミン神経細胞から，辺縁系ことに側坐核に投射する神経回路が担っていると考えられる[7]（**図1**）．

さらに最近は分界条床核（bed nucleus of the stria terminalis: BNST），扁桃体中心核，側坐核内側移行帯などの拡張扁桃体とよばれる辺縁系の脳部位が，依存性薬物の報酬に関わっていると注目されている[9]．前頭前野皮質に投射する神経回路は薬物誘発性の薬物再摂取，外側基底扁桃体に投射する神経回路は手がかり誘発性の薬物再摂取に関与し，渇望状態，つまり薬物摂取を期待している状態には重要な役割を果たしている．

中枢神経刺激薬の標的分子

モノアミントランスポーターは，神経終末から放出されたモノアミンであるドパミン（DA），ノルエピネフリン（NE），セロトニン（5-hydroxytryptamine: 5-HT）を神経終末に再取り込みし，神経伝達を終了させる[1]（**図2**）．細胞膜モノアミントランスポーターは，神経終末の細胞膜に存在し，Na^+/Cl^-依存的にモノアミンを神経終末内に取り込む膜蛋白で，アミノ酸トランスポーターなどとともにSLC6（solute carrier 6）とよばれる遺伝子ファミリーを形成している[12]．コカインはモノアミントランスポーターに結合して再取り込みを阻害し，シナプス間隙に放出されたモノアミンの濃度を増加させることにより効果を及ぼす．一方，メタンフェタミンは細胞膜モノアミントランスポーターに取り込まれる際にモノアミンを放出するとともに，シナプス小胞のモノアミントランスポーターにも作用し，シナプス小胞内のモノアミンの細胞質内への放出を促進する2つの作用機序を持つ[1]．シナプス小胞モノアミントランスポーター（vesicular monoamine transporter: VMAT）は，DA，NE，セロトニン，ヒスタミンすべてを基質とする単一の蛋白で，神経終末内のシナプス小胞膜に存在し，シナプス小胞アセチルコリントランスポー

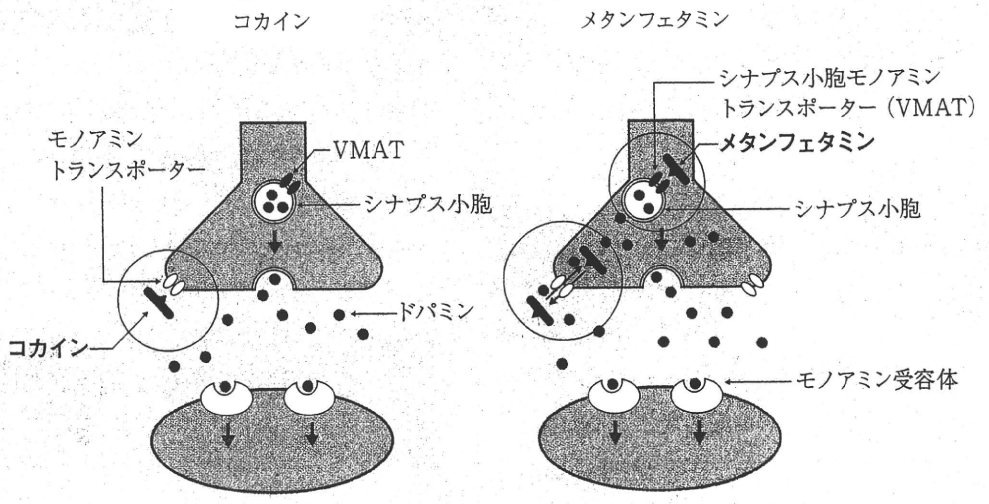

図2　中枢神経刺激薬の薬理作用
コカインは細胞膜モノアミントランスポーターに結合して再取り込みを阻害し，メタンフェタミンはシナプス小胞のモノアミントランスポーターにも作用し，シナプス間隙のモノアミンを増やす．
（Fleckenstein AE, et al, 2003[10], Fone KC, et al, 2005[11] より）

タ　ー（vesicular acetylcholine transporter: VAChT）とともにSLC18（solute carrier 18）とよばれる遺伝子ファミリーを形成している[12]．コカインの類似化合物質はモノアミントランスポーターの一つであるドパミントランスポーターに結合親和性が強いほど，報酬効果もより強いことが知られている[13]．

ドパミントランスポーター遺伝子改変マウスモデル

コカインはドパミントランスポーター（dopamin transporter: DAT），セロトニントランスポーター（serotonin transporter: SERT），ノルエピネフリントランスポーター（norepinephrine transporter: NET）のいずれにも作用するが，その主たる作用部位を明らかにするためにモノアミントランスポーター欠損マウスを用いてコカインの作用機序が検討された[14]．DAT欠損マウスは野生型マウスにくらべて3～6倍のきわめて活発な運動量を示し，ドパミン再取り込み機能の欠如が，ドパミン合成酵素，ドパミン受容体のダウンレギュレーションにおいても代償できなかったことを示している．また，SERT，NETの発現に代償性の変化はみられなかった．しかし，コカイン，アンフェタミンの投与により野生型マウスでみられる運動量の増加作用は，DAT欠損マウスにおいては消失していることから，中枢神経刺激薬の運動量増加作用にはDATが不可欠であることが示唆される[14]．

コカインの報酬は3種類のモノアミントランスポーターの中でもDATを介しているというDAT仮説が想定されてきたが，DAT欠損マウスにおいて条件づけ場所嗜好性試験（conditioned place preference: CPP）のコカインの報酬が保たれていた[14,15]．しかし，CPPにおけるコカインの用量によって野生型マウスとDAT欠損マウスでは若干の違いが報告され

た．コカインCPPは野生型マウスでは低用量と高用量ともに観察されたが，DAT欠損マウスでは高用量においてのみみられた[14]．また，遺伝的背景が異なるとCPPに影響を及ぼすこともわかった．DAT欠損マウスの遺伝背景がC57BL/6[16,17]あるいはDBA/2J[17]の純系の場合には雑種（混合遺伝背景）よりもコカインCPPが減少していた．CPPとは異なりDAT欠損マウスは“常に”コカインを静脈内自己投与（intravenous self-administration〈SA〉）しなかった[18]．

最近，DATの発現を完全欠損させるのではなく増減させた遺伝子改変マウスが作製された．DATを過剰発現させたマウスではコカインCPPが増強していたが，コカインによる移所運動量に変化をもたらさなかった[19]．DAT発現が90%少ないDATノックダウンマウスが，DATプロモーター配列の下流にDATの相補的DNA（complementary DNA: cDNA）を挿入して作製された[20]．DATノックダウンマウスではDAT発現の著しい減少により細胞外ドパミンのクリアランスが低下し，細胞外ドパミン濃度をわずかに上昇させた．DAT完全欠損マウスとは対照的にDATノックダウンマウスでは低用量のコカイン投与で移所運動量の増加を示したが，コカインCPPには変化がなかった．

DAT欠損マウスは中枢神経刺激薬の作用機序の解明に有用なモデルだが，ドパミン神経伝達を大きく変化させる．最近の遺伝子改変技術はそのような大きな変化を引き起こさないモデルマウスの作製を可能とした．マウスDATの第二膜貫通領域のアミノ酸配列はコカインの高親和性結合に重要な役割を果たしている．そこで第二膜貫通領域のアミノ酸配列を変異させコカインへの感受性が80倍低下しているがドパミンの再取り込みにはほとんど影響を及ぼさない変異DAT蛋白を持つDATコカイン非感受性（DAT-“cocaine-insensitive”〈CI〉）マウスが作製された[21]．DAT-CIではドパミン取り込み動態の変化は少ないが，コカインは細胞外ドパミン濃度を上昇させず，ドパミン細胞の発火に影響しなかった．DAT欠損マウスと同様に新奇環境での移所運動量の増加はDAT-CIマウスで観察されたが，コカインは移所運動量を減少させた．しかし，DAT-CIマウスではコカインによるCPP，静脈内自己投与や常同行動を含むコカイン誘発性行動の多くは消失していた．DAT-CIマウスにおいてはコカインが側坐核での細胞外ドパミンを上昇させなかったことから，コカインによる側坐核での細胞外ドパミンの増加がコカイン報酬には重要であることを示している．

これらのDATを欠損，あるいは過剰発現させた遺伝子改変マウスモデルの解析により，コカインの報酬効果にはDATの発現が重要な役割を果たすことが明らかとなった．

ドパミン以外の神経伝達系の関与

一方，他のモノアミントランスポーター欠損マウスにおけるコカインの報酬効果については，SERT，NETが欠損するとCPPによるコカイン報酬効果はかえって増加する結果が得られた[14,16]．さらにfluoxetineによるSERT阻害またはnisoxetineによるNET阻害はDAT欠損マウスでCPPによる報酬効果を示した[22]．DATの欠損に加えて他のモノアミントランスポーターの阻害によりfluoxetineやnisoxetineが報酬効果を示した結果は，SERT，NET欠損によるコカイン報酬効果の増加と一致する方向であった．実際，SERTの阻害薬の投与はコ

カインと同程度に，DAT欠損マウスにおける側坐核[23]と線条体[24]において細胞外ドパミンを増加させた．これらの結果はDAT欠損マウスにおける腹側被蓋野でのドパミン神経の活動をセロトニン神経系が制御している可能性を示唆している．ドパミンとセロトニン神経系の相互作用が報酬のメカニズムに関与している結果が，ドパミンが減少しているマウスモデルの解析によっても得られた．ドパミン減少マウスはドパミン神経のみでカテコラミン生合成の律速酵素であるチロシンヒドロキシラーゼを欠損させて作製された[25]．ドパミン減少マウスでは，DAT欠損マウスと同様にfluoxetineによるSERT阻害によりCPPにより報酬効果が示された．コカインの報酬効果は，DAT，SERT，NETがそれぞれ単独に欠損しても，他が代償することで保持されると考えられる．そこで次にDATとSERTのダブル欠損マウスを作製して検討した．コカインの報酬効果はDATが完全欠損し，SERTが完全欠損，あるいは部分欠損している遺伝型マウスでは消失した．しかし，SERTが完全欠損していても，DATが部分欠損の場合では保持された[26]．これらの結果により，コカイン報酬にはDATとSERTがともに関与し，SERTよりもDATが，より大きな役割を果たしていると考えられた[27]．さらにセロトニン1B受容体作動薬はコカインによる報酬効果を増強させ，また側坐核へのドパミン放出を増加させることが示された[15]．セロトニン1B欠損マウスは野生型と比較してコカインにより惹起される運動量がより多く増加し，また静脈内自己投与試験においてもコカインへの報酬が増強していることが報告された．またアンフェタミンの急性あるいは反復投与による行動感作の発展が野生型マウスに比してより促進される効果も観察された．

これらの結果はドパミン神経伝達を制御するセロトニン系などの他のモノアミン神経系が中枢神経刺激薬依存の病態に関与していることを示している[28]．

オピオイドの標的分子

モルヒネに代表されるオピオイドの標的分子としてオピオイド受容体が遺伝子クローニングによりG蛋白に共役する7回膜貫通型遺伝子ファミリーの一つとして同定された[2]．オピオイド系は，μ，δ，κと名づけられた3種類の受容体と，構造的に似通ったエンドルフィン，エンケファリン，ダイノルフィンなどの内因性オピオイドペプチドファミリーから成り立つ．オピオイド受容体は，オピオイドの脳内報酬系への作用部位であると考えられている．3種類のオピオイド受容体の中でもμ受容体はγ-アミノ酪酸（γ-aminobutyric acid: GABA）系介在神経，腹側被蓋野に投射されるGABA神経終末に発現し，オピオイドがこれらのμ受容体に結合することによりGABAの放出が抑制された結果，ドパミン神経伝達を増強させると考えられている．

さらに，μオピオイド受容体欠損マウス[29]では，静脈内自己投与試験，CPPにおいて，モルヒネの報酬効果が消失していた[30]．これらの報酬試験の結果からδおよびκ受容体が正常に発現しているμ欠損マウスでは，モルヒネの報酬効果はδあるいはκ受容体ではなくμ受容体を介していると考えられる．さらに，μ欠損マウスではコカインやエタノールの報酬効果が減少していたことは，モルヒネのみならず他の依存性薬物の報酬効果にもμオピオイド受容体が関与していることを示唆している[31]．このように依存性薬物の標的分子の欠損マウスモ

デルの解析により，ドパミン神経伝達に加えてオピオイド系が薬物依存の病態に関与していることが示された．

神経可塑性と行動感作

依存性薬物を反復使用しているうちに依存が形成・強化される．依存性薬物による報酬効果は繰り返し学習されることにより形成されることから，薬物依存の病態の基礎として神経可塑性が重要と考えられている．実際，記憶・学習に関与する*N*-メチル-D-アスパラギン酸（*N*-methyl-D-aspartic acid: NMDA）型グルタミン酸受容体の拮抗薬の投与は薬物依存の形成を抑制する．メタンフェタミンやコカインといった中枢神経刺激薬を反復投与すると，惹起される異常行動が進行性に増大する現象が知られており，この薬物反応の増強は行動感作（逆耐性現象）として知られている[32]．通常は，同じ量を繰り返し摂取していると耐性が生じるが，中枢神経刺激薬では反対によく効くようになり，耐性の反対という意味で逆耐性現象と名づけられている．

行動感作（逆耐性現象）はいったん形成されると長期に断薬しても薬物再投与で容易に再現され，脆弱性が増強していると考えられる[33]．依存性薬物は直接，間接にドパミン神経伝達を増強させることにより報酬効果を示すことから薬物依存が形成されるにはドパミン神経伝達の増強が必要だが，依存が形成された後にはドパミン系を制御する神経伝達の神経可塑性が変化していると考えられる．つまり，薬物依存の初期と強化・維持期では，その神経機序は異なると考えられる．中脳辺縁系ドパミン経路の活性化は依存の初期に重要であり，強化・維持期にはドパミン経路に加えて前頭前野，扁桃核，海馬から側坐核へのグルタミン酸経路の活性化が重要と考えられている．

脆弱性要因としてのストレス

ストレスは薬物依存の発症のみならず再燃の脆弱性に関わっていることが知られている[34]．ストレスが薬物依存の病態に関与するメカニズムとしてストレスによる緊張を緩和するために依存性薬物を使用することが考えられている[35]．たとえば，肉親の喪失や虐待の体験，あるいは日常生活上のさまざまな負担さえも薬物依存の発症の脆弱性要因となりうることが報告されている．動物モデルを用いた研究では，フットショックや拘束などの身体ストレス，社会的隔離や敗北などの心理ストレスが依存性薬物の自己投与や薬物探索行動を増強することが報告されている．この脳内ストレス系は脆弱性要因として薬物依存のメカニズムに関与していると考えられる．

最近の研究成果により，従来から依存性薬物の強化効果に関連していると考えられている神経伝達物質（ドパミン，オピオイドペプチド，セロトニン，GABA およびカンナビノイド）だけではなく，脳内ストレス系に関与していると考えられるコルチコトロピン放出因子（corticotropin-releasing factor: CRF），ノルエピネフリンおよびニューロペプチド Y（neuropeptide Y: NPY）も薬物の依存形成に関わっていることが示された[36,37]．依存性薬物の慢性投与は副腎皮質刺激ホルモンを上昇させ，CRF が介する視床下部-下垂体-副腎系と脳内ストレス反応系の調節を障害し，依存性薬物の急性退薬も，分界条床核（BNST）でノルエピネフリンの放出を増加させ，扁桃体の内側

核のNPYを減少させることが明らかとなった．

ゲノムワイドによる遺伝子多型解析

薬物依存の発症要因として，外因物質である依存性薬物に加えて遺伝的要因も関与する．遺伝的要因が薬物依存の発症に関与することは双生児と養子研究などから推測され，薬物依存発症の一致率は二卵性双生児に比べて一卵性が高い．さらに養子研究から，生父が薬物依存の養子は，そうでないものに比べ薬物依存の発症率が高いことが知られている．遺伝的に個体差がないマウスの純系統種においても，系統間で依存性薬物に対する反応が異なることが知られている．薬物依存の原因となる遺伝要因は，他の身体疾患と同様に標的分子をコードする単一の遺伝子だけではなく，複数の遺伝子が関与していると考えられる[38,39]．遺伝負因を持つことは必ず薬物依存の発症に結びつくものではない．つまり，遺伝負因の意味するところは，薬物を使用した者のうちで依存発症の準備状態と考えられる遺伝的脆弱性を形作るものと思われる．

メタンフェタミン依存患者ではモノアミン関連分子（受容体，トランスポーター，代謝酵素）を中心にゲノムの遺伝子多型が解析されている[40]．モノアミン神経系と相互作用している神経系や他の依存性薬物の作用する神経系に関係するもの，メタンフェタミンが神経毒性を示すことから細胞傷害性に関わる遺伝子群，薬物代謝に関わる遺伝子群，そして中枢神経刺激薬精神病と統合失調症との症状の類似性から類推される遺伝子群などに大別される．いずれにおいてもおよそ半分の遺伝子で相関性が認められており，他の動物実験などから関連性のあると考えられる遺伝子についてはメタンフェタミン依存と遺伝子多型との相関が高いと思われる．多くの人種で解析された遺伝子は少ないが，なかでもよく解析されているのはドパミンD_2受容体（*DRD2*）遺伝子である．*DRD2*遺伝子多型は日本人と韓国人ではメタンフェタミン依存との相関が認められた[41,42]．さらに臨床表現型にも注目された解析がなされており，*DRD2*遺伝子は初回使用から精神病性障害発症までの潜時に，DATは治療予後[43]に，catechol-*O*-methyltransferase（*COMT*）遺伝子は自然再燃などとの関連性[44,45]が指摘されている[46,47]．

個別の遺伝子多型に注目した解析では多くの遺伝子について調べることに限界があるため，ゲノム全体を網羅した解析が望まれていた．本邦の研究グループ（Japanese Genetics Initiative for Drug Abuse: JGIDA）と米国国立薬物依存研究所（National Institute on Drug Abuse: NIDA）との共同研究によりゲノムワイド相関解析（genome-wide association: GWA）研究が行われ，これまで注目されてこなかった多数の分子にメタンフェタミン依存との相関性が認められた[48]．このゲノムワイド相関解析により，神経シナプス形成分子，神経成長関連分子，神経可塑性関連分子，神経細胞接着関連分子などが脆弱性候補遺伝子として示された．薬物依存発症の脆弱性は，これら複数の遺伝子が関与していると考えられる．

おわりに

薬物依存の形成には報酬のメカニズムに重要な役割を果たす中脳辺縁系ドパミン経路が関わっていると考えられてきた．依存性薬物の標的分子の欠損マウスモデルの解析により，ドパミン以外の神経伝達系により制御されるなど薬物依存の病態機序が明らかにされてきた．さらに薬物依存患者におけるゲノムの遺伝子多型解

析などにより，今後，薬物依存の病態における新たなメカニズムが解明され，予防・治療法の開発に貢献することが期待される．

（曽良一郎，氏家　寛）

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物質依存の認知科学

物質依存は，依存形成能を有する化学物質と，そのような化学物質へのなんらかの摂取欲求を持った人とが遭遇するところに生まれる．

その摂取欲求は，当初は小さなものかもしれないが，化学物質の自覚効果を「快」と感じることや，物質摂取によって精神的な苦痛が軽減できたと認識することなどによって徐々に大きくなる．機会的な物質摂取が反復的になるにつれて，物質効果の離脱に伴う憂うつ感や罪責感が大きくなり，そうした否定的気分からの逃避もさらなる物質摂取の動機になる．こうして摂取欲求は強迫的となり，その段階まで進行すると，物質の効果と連合したさまざまな環境刺激が物質摂取に対する渇望を誘発するきっかけになる．

この一連のプロセスは，認知行動科学的には「学習」の一種として理解できるものである．「学習」とは，経験の結果によって比較的永続的に行動が変化することをいう．すなわち「学習」という意味は，環境に適応するために合理的な行動を身につけるということばかりではない．自己および他者にとって困った帰結を導いてしまうような行動変化も学習によって獲得されたものである．したがって依存を認知行動科学的に理解するためには，まず学習の原理を理解する必要がある．

学習の二大原理が「オペラント条件づけ」と「古典的条件づけ」である．

オペラント条件づけとは，行動に随伴してなんらかの事象を生起させ，その行動の頻度を増加させたり減少させたりする手続きをいう．日常生活の行動の多くがオペラント条件づけで形成・維持されている．動物実験では**図1**に示すような実験箱に動物を入れ，小さなレバーを押せば餌や水などが与えられるようにしておく．この方法で客観的・定量的に条件づけの分析ができる．行動の頻度を増やす操作を強化，減らす操作を罰という（**表1**）．このような動物実験で，依存形成能を持つ薬物の多くが自発的な摂取行動の頻度を増加させることが確かめられている．この実験では動物の静脈内あるいは胃内にカテーテルを留置し，動物が自発的にレバーを押すと少量の薬液が体内に注入されるようにしておく．コカインやモルヒネでは**図2**に示すように摂取頻度が増える．このような薬物効果を薬物の「強化効果」といい，依存形成能の判定には最も重要な効果である[1]．

古典的条件づけとは，生得的にある種の行動

White Matter Abnormalities as a Risk Factor for Postoperative Delirium Revealed by Diffusion Tensor Imaging

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Objective: *Delirium is a common and critical clinical syndrome in older persons. The authors examined whether any abnormalities in the white matter (WM) assessed by diffusion tensor imaging (DTI) predisposes patients to develop delirium after cardiac surgery and also analyzed other risk factors for delirium.* **Method:** *In 116 consecutive patients who underwent scheduled cardiac operations, fractional anisotropy (FA) values obtained by DTI before the surgery and pre-, peri-, and postoperative factors were evaluated. The postoperative delirium was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for delirium.* **Results:** *Delirium developed in 19 of 116 patients (16.4%). Eighteen of the patients with delirium (94.7%) were older than 60 years. A multivariate logistic regression analysis showed that advanced age and poor performance on a semantic fluency task (the Word Fluency test animal) were important predictive indicators of the delirium. In addition, a voxel-by-voxel analysis using the Statistical Parametrical Mapping 2 revealed that the FA values of the patients with postoperative delirium were significantly lower than those of the nondelirium patients in the bilaterally widespread deep WMs and bilateral thalamus, whereas the analysis treating age as a nuisance variable indicated a significant change in only four clusters of the brain areas, e.g., the left frontal lobe WM, and left thalamus, when compared with the nondelirium group.* **Conclusion:** *The abnormalities in the deep WMs and thalamus that were mainly accelerated by aging may account for the vulnerability to postoperative delirium, and the semantic word fluency could be a useful predictive indicator of delirium.* (Am J Geriatr Psychiatry 2010; 18:743–753)

Key Words: Delirium, diffusion tensor imaging, word fluency test, white matter

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Delirium is a neurobehavioral syndrome associated with disturbances in consciousness and attention.[1,2] The symptoms of delirium involve an acute generalized impairment of cognitive function (orientation, memory, and abstract thinking), behavioral and psychomotor abnormalities (ranging from apathy and agitation), an altered sleep–wake cycle, and disorganized thinking.[3–5]

Delirium occurs in older hospitalized patients at a higher rate of incidence. The prevalence of delirium at hospital admission ranges from 14% to 24%, and the incidence of delirium during hospitalization ranges from 6% to 56% among the general hospital populations. In particular, delirium occurs in 15%–53% of older postoperative patients.[5] The etiology of delirium may be a complex and multifactorial syndrome.[3,6] It has been reported that the postoperative delirium can be attributed to precipitating factors, e.g., surgery and intercurrent illness, and risk factors predisposed to individual patients including older age, cognitive impairments, sensory impairments, and coexisting medical conditions.[6–11] Circumstantial evidence suggests that advanced age, decline of the cognitive functions, and increased vascular changes are primarily involved in the vulnerable conditions to delirium.[5,12,13]

Magnetic resonance diffusion tensor imaging (DTI) is a noninvasive in vivo method for characterizing the integrity of anatomical connections and white matter (WM) circuitry and provides a quantitative assessment of the microstructure of the WM, e.g., myelin sheath and intra-axonal structures.[14] The diffusion properties that are sensitive to water diffusion can be assessed by means of two indices: fractional anisotropy (FA) and mean diffusivity (MD). FA is a quantitative measure of the anisotropy calculated from the DTI and reflects the degree of directionality of cellular structures within the fiber tracts, whereas MD is a measure of diffusion in the nonlinear direction or free diffusion.[15] FA rather than MD had been used in many studies examining an age-related change in the WM DTI in normal healthy adults,[16–21] with correlation to a decrease in the cognitive function.[22–24] The changes in the WM shown by the FA studies suggest that a deterioration in the cortical circuitry with aging are attributed to the age-related cognitive decline.[25,26]

This study had two primary aims. The first was to examine whether any changes in the WM indicated by FA were predisposed in the patients who developed to delirium after cardiac surgery. We assumed that abnormalities in the WM is involved in the vulnerability to the development of postoperative delirium. The second aim was to investigate whether pre-, peri-, and postoperative risk factors for delirium reported in previous studies[6–13] also behave as a risk factor in this study.

This study demonstrated that there were a widespread reduction of the FA values in the brain of patients with postoperative delirium compared with the nondelirium patients and that advanced age and a neuropsychological test, the Word Fluency test animal (WFTA) were evaluated as important indicators of postoperative delirium. In addition, we analyzed relationships of the age between the FA values, because an age-related linear decline of the FA values was indicated by several studies.[17–19,21–23]

METHODS

Subjects

Subjects were 119 consecutive Japanese patients that underwent scheduled cardiac operations between August 2005 and August 2006 in the Department of Cardiothoracic Surgery, Tokyo Medical and Dental University, University Hospital Faculty of Medicine (Tokyo). Patients who were admitted for an emergency operation in this period were excluded from this study. Approval was obtained from the ethics committee of Tokyo Medical Dental University, and all patients gave written informed consent.

All the patients received an assessment battery for preoperative conditions and a magnetic resonance imaging (MRI) study, whereas 18 of the subjects who did not accept to be examined by a neuropsychological test battery were evaluated by the preoperative assessments excluding the neuropsychological tests. After the operation, all the patients were assessed daily not only by the medical staff of the Department of Thoracic Cardiovascular Surgery but also by a well-trained psychiatrists (either the principle investigator [AS] or a coauthor [TT]) until discharged. The presence of delirium was determined by the psychiatrists according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-TR criteria for

delirium.[1,27,28] The severity of delirium was evaluated using the severity items of the Delirium Rating Scale—Revised-98.[29]

Preoperative Evaluations

The preoperative evaluation included medical history, impairments in their physical condition, handicaps, alcohol consumption, and smoking habits. Neuropsychological tests, i.e., the Mini-Mental State Examination,[30] the Trail Making tests A and B,[31] the Stroop Color-Word interference test,[32] Word Fluency tests of animal and letter,[33] digit spans of forward and backward, and the Beck Inventory Depression Scale,[34] were examined on the day after the admission for surgery. For the WFTA, participants were asked to name as many animals as possible for 60 seconds. For the Word Fluency test K, participants were asked to name as many words as possible beginning with the letter "Ka (in Japanese)" for 60 seconds.

Peri- and Postoperative Evaluations

The operating procedure, operation time, anesthetic time, use of extracorporeal circulation, amount of blood loss, and requirement of blood transfusion during the surgery were obtained from the flow chart. The postoperative medical factors for the intensive care and any cardiopulmonary complications were also included in the analyses for the risk factors of delirium. No subjects in the study received opioid analgesics or dexmedetomidine (α_2-adrenergic agonist)[35] during the peri- and postoperative period.

Magnetic Resonance Imaging

DTI was performed using a 1.5-tesla General Electric Signa (General Electric, Milwaukee) with a standard head coil. Diffusion weighted echo planar images were acquired in the axial plane (repitition time [TR] = 8,000 milliseconds, echo time [TE] = 78 milliseconds, matrix = 128 × 128, field of view [FOV] = 24 cm × 24 cm, slice thickness = 5 mm, interleave, number of excitations [NEX] = 4) providing whole brain coverage. Six noncollinear directions were sampled using *b* values from 0 to 1,000 s/min and one additional image with a *b* value of zero. The imaging time for the DTI examination was 7.5 minutes. The images were corrected by the GE workstation for eddy current disorientations. Conventional axial T1 and T2-weighted images were also performed to assess WM lesions or lacunar infractions. All subsequent sequences were aligned with the anterior and posterior commissure (AC-PC) plane.

FA was calculated from the diffusion weighted images using the method proposed by Pierpaoli and Basser.[36,37] The FA data were normalized to the Montreal Neurological Institute space using the general linear deformation by Statistical Parametrical Mapping 2 (SPM2, Wellcome Department of Cognitive Neurology, London)[38] as described in the previous reports.[39,40] The FA maps were smoothed with a Gaussian kernel of 12 mm full width at half maximum. The resultant FA values were compared between two groups (patients with or without postoperative delirium) by a voxel-by-voxel analysis using the SPM2. First, to estimate the population effects (diagnostic effects), we used a single subject condition (nondelirium or delirium) and covariate (no covariate of interest) model for the SPM analysis. We next applied the single subject condition (nondelirium or delirium) and covariate (age). For the analyses, we used the one-tailed $p < 0.001$ (uncorrected) as a statistical threshold to search for significant differences between the groups, as we hypothesized that there were reductions in the FA values of patients with postoperative delirium. The voxel-by-voxel analysis in the stereotactic space can provide an unprejudiced view of the result, whereas a region-of-interest technique is limited by the fact that the selection of sample depends on the observer's priori choice and hypothesis. However, image misregistrations from spatial normalization in the voxe-by-voxel analysis can mimic FA alterations, if there are large variations of brain shape in older subjects.[14,41] Thus, we set the masking threshold for the FA values of 0.2 to exclude voxels containing the partial volume of WM and other tissues and to minimize the effect of the misregistrations.

Statistical Analysis

We compared the pre-, peri-, and postoperative factors and the neuropsychological assessments between the delirium group and the nondelirium group. The continuous variables are expressed as the mean ± SD, and the categorical data are expressed as

TABLE 1. Comparisons of Pre-, Peri-, and Postoperative Variables Between the Delirium Group and the Nondelirium Group (Univariate Analysis)

Preoperative Data	Delirium Group (n = 19)	Nondelirium Group (n = 97)
Age	73.1 ± 6.4	62.5 ± 11.8[a]
Sex (male)	13 (68.4%)	65 (67.0%)
Body mass index	21.6 ± 3.0	23.6 ± 3.0[b]
Hypertension	18 (94.7%)	65 (67.1%)[c]
Diabetes mellitus	6 (31.6%)	40 (41.2%)
Hemodialysis	5 (26.3%)	5 (5.2%)[c]
Hypercholesteremia	6 (31.6%)	39 (40.2%)
Cerebral vascular disease	2 (10.5%)	15 (15.5%)
Smoking (cigarette/day × year)	647.2 ± 538.9	433.2 ± 713.7
Alcohol daily use	9 (50%)	32 (34%)
Visual disturbance	1 (5.3%)	5 (5.2%)
Auditory disturbance	2 (10.5%)	2 (2.1%)
History of cancer	3 (16.7%)	12 (12.4%)
Cognitive tests[d]		
Mini-Mental State Examination	26.3 ± 3.4	27.2 ± 2.7
Trail making test B-A (seconds)	155.9 ± 131.5	82.3 ± 125.2[c]
Color Stroop test (seconds)	21.4 ± 14.3	18.9 ± 15.9
Word fluency test animal	13.4 ± 4.1	18.6 ± 5.8[a]
Word fluency test "Ka (in Japanese)"	7.6 ± 3.4	10.0 ± 4.2[c]
Digit span forward	7.8 ± 2.4	8.2 ± 2.0
Digit span backward	5.2 ± 1.9	5.9 ± 2.3
Perioperative data		
Operation time (minutes)	404.7 ± 89.2	408.6 ± 113.5
Anesthetic time (minutes)	510.9 ± 92.8	515.4 ± 117.0
Extracorporeal circulation (on)	10 (52.6%)	60 (61.9%)
Blood loss (mL)	797.7 ± 559.4	988 ± 995.1
Blood transfusion	12 (66.7%)	40 (41.2%)[c]
Type of operation		
Coronary artery bypass graft (CABG)	7 (36.8%)	47 (48.5%)
Valve replacement (VR)	5 (26.3%)	24 (24.7%)
CABG + VR	3 (15.8%)	9 (9.3%)
Thoracic aortic aneurysm	3 (15.8%)	9 (9.3%)
The others	1 (5.3%)	8 (8.2%)
Postoperative data		
Incubation period (days)	1.5 ± 1.6	1.3 ± 1.8
Intensive care unit stay (days)	4.2 ± 2.1	4.6 ± 8.3
Cardiopulmonary complication	11 (61.2%)	59 (60.8%)

Notes: Continuous variables are expressed as mean ± SD, and categorical data are expressed by the number of patients. The two-tailed Student's *t*-test or the Mann-Whitney *U* test was used for the continuous variables. The comparison of proportions was analyzed by the χ^2 tests. If the expected cell frequencies were <5, we used Fisher's exact test for the analysis.

[a]$p < 0.001$.

[b]$p < 0.01$.

[c]$p < 0.05$.

[d]The results of the cognitive tests were obtained from 17 patients with delirium and 81 patients with nondelirium (see Methods).

proportions. The two-tailed Student's *t*-test or the Mann-Whitney *U* test was used for the continuous variables. The comparison of proportions was analyzed by the χ^2 tests. If the expected cell frequencies were <5, we used Fisher's exact test for the analysis. The variables with a p value <0.05 were entered into a backward stepwise logistic regression analysis requiring a p value less than 0.05 to remain. In addition, a comparison between the two groups using analysis of covariance (ANCOVA) with the age of the patients treated as nuisance covariate and a correlation analysis with the age were performed. A correlation with the age was analyzed by the Pearson test. The statistical analyses were carried out using the SPSS version 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

General

Of the 119 patients, we eliminated three patients, who had a cerebral vascular embolism after the surgery, from the statistical analyses of this study. The mean age of all the patients (F/mean = 38/78) was 64.3 (27–84 years). Nineteen of the 116 patients (16.4%) developed delirium after the cardiac surgery. The mean ± SD of the severity score of Delirium Rating Scale—Revised-98 was 24.3 ± 6.0. Eighteen of the patients with delirium (94.7%) were older than 60 years, whereas 60 of 97 nondelirium patients (61.9%) were older than 60 years. The patients underwent five types of cardiac surgery (number of patients): coronary artery bypass graft surgery (54), valve replacement surgery (29), coronary artery bypass graft surgery and valve replacement surgery (12), thoracic aortic aneurysm surgery (12), and the others (9). The cardiac surgery using extracorporeal circulation was carried out on 70 patients (60.3%).

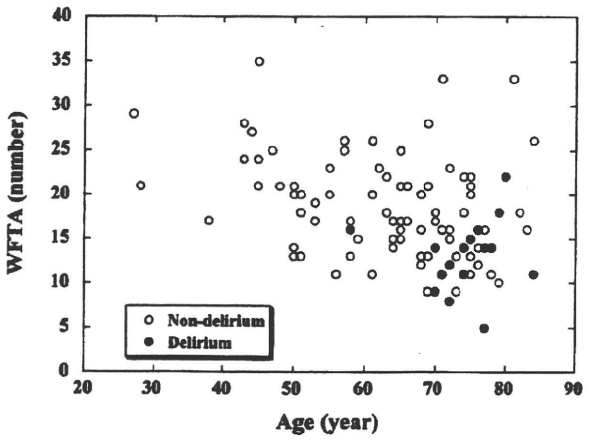
Pre-, Peri-, and Postoperative Variables

The results of the comparison of the pre-, peri-, and postoperative data between the delirium group and the nondelirium group are shown in Table 1. There was a statistically significant difference between the two groups in age, body mass index, high blood pressure, hemodialysis, and blood transfusion

during the operations. Based on the neuropsychological tests, a significant difference between the two groups was observed in the WFTA, the Word Fluency test K, and the Trail Making test B-A, but not in the Mini-Mental State Examination, Color Stroop test, or digit span tests. There was no patient who had a depressive syndrome checked by either the Beck depression scale or a preoperative interview. Neither alcoholic nor dementia was diagnosed by the preoperative assessment in the subjects of the study.

The multivariate logistic regression analysis, in which the significant variables with a $p < 0.05$ based on the univariate comparison test were entered, revealed that advanced age and low WFTA score were important risk factors of postoperative delirium (Table 2). The analysis using ANCOVA with the age of the patient treated as a nuisance covariate showed that the WFTA score of the delirium group was significantly lower than that of the nondelirium group ($F = 5.82$, $df = 1,95$, $p < 0.05$, Fig. 1).

FIGURE 1. Scatter Plots of the Word Fluency Test Animal (WFTA) With Age in Patients With Delirium and Without Delirium



The WFTA score of the delirium group was significantly decreased ($F = 5.82$, $df = 1,95$, $p < 0.05$) compared with that of the nondelirium group. The analysis was performed by ANCOVA with the age of the patient treated as a nuisance covariate.

MRI Study

The comparison of the FA values between the delirium group and nondelirium groups using a single subject condition without the covariate model for the SPM2 is shown in Fig. 2 and Table 3. There was a significant reduction in the FA values of the delirium patients in many sections of the bilateral WM, i.e., frontal lobe, temporal lobe, parietal lobe, limbic lobe, and the bilateral thalamus.

The SPM2 analysis between the two groups with treated age as the covariate demonstrated a significant decrease in the FA values in four clusters of the brain area, i.e., left subgyral of frontal lobe, right cingulate gyrus, left ventral anterior nucleus of the thalamus, and corpus callosum (Fig. 3 and Table 3). The analysis using ANCOVA also indicated that the FA values of the delirium group was significantly decreased in the four brain regions compared with the nondelirium group (left thalamus (ventral anterior nucleus): $F = 11.13$, $df = 1,113$, $p < 0.01$, left frontal lobe (subgyral): $F = 11.87$, $df = 1,113$, $p < 0.001$, right cingulate gyrus: $F = 11.94$, $df = 1,113$, $p < 0.001$, corpus callosum (splenium): $F = 10.00$, $df = 1,113$, $p < 0.01$). In addition, a statistically significant correlation between the FA values and the age was found in all four areas of the nondelirium group (left frontal lobe [$r = 0.394$, $df = 95$, $p < 0.0001$], right cingulate gyrus [$r = 0.376$, $df = 95$, $p < 0.0001$], left thalamus [$r = 0.488$, $df = 96$, $p < 0.0001$] and corpus callosum [$r = 0.398$, $df = 95$, $p < 0.0001$]) but not either of the brain areas of the delirium group (Fig. 4).

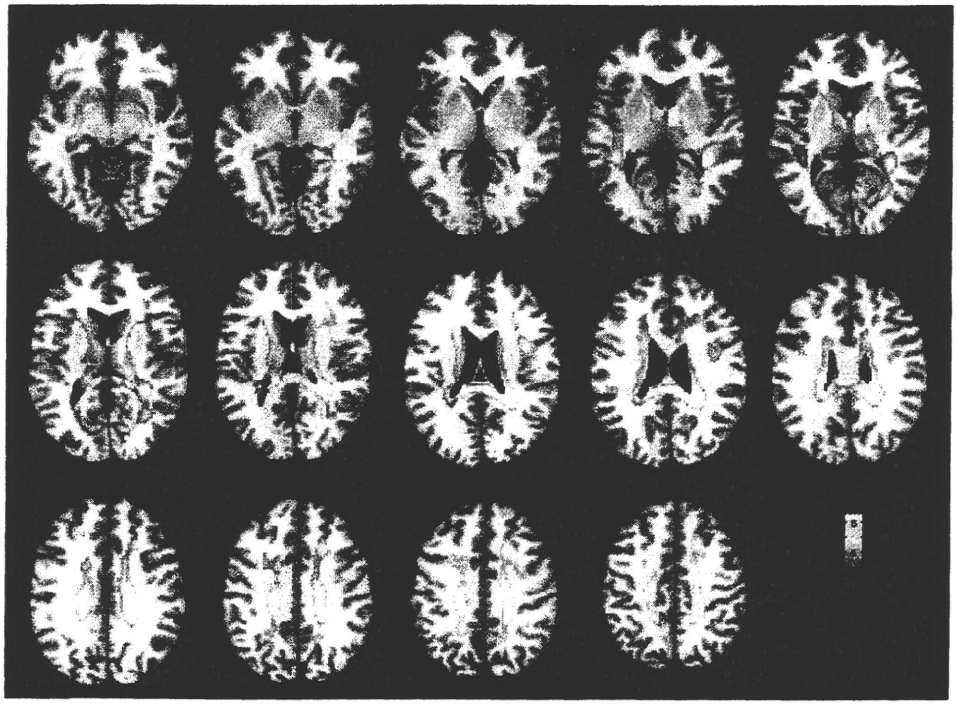
In a subgroup of the subjects older than 60 years, the analysis using ANCOVA also indicated that the FA values of the delirium group was significantly decreased in the four brain regions compared with the nondelirium group (left thalamus (ventral anterior nucleus): $F = 14.6$, $df = 1,74$, $p < 0.01$, left frontal lobe (subgyral): $F = 10.8$, $df = 1,74$, $p < 0.01$, right

TABLE 2. Predictive Factors of Delirium After Cardiac Surgery Resulting From the Multivariate Logistic Regression Analysis

Variables	Odds Ratio	95% Confidence Interval	p
Age (per year)	1.163	1.044–1.296	0.006
WFT A (per number)	0.827	0.707–0.966	0.017

Notes: Variables with significantly different changes between the delirium group and the nondelirium group ($p < 0.05$), i.e., age, body mass index, high blood pressure, hemodialysis, Trail making test B-A, WFTA, WFTK, and blood transfusion, were entered into a backward stepwise logistic regression analysis requiring a p value < 0.05 to remain (Wald χ^2 test, $df = 1$).

FIGURE 2. Comparisons of FA Values Between the Delirium Group and Nondelirium Group by a Single Subject Condition Without the Covariate Model for the SPM2



The SPM{t} values (one-tailed p <0.001, uncorrected) are displayed on the axial FA template images. A significant decrease in the FA values for the delirium group was observed in many brain areas including the bilateral thalamus, bilateral deep white matters of entire cerebral cortices, and corpus callosum.

cingulate gyrus: $F = 7.4$, $df = 1,74$, $p < 0.01$, corpus callosum (splenium): $F = 9.9$, $df = 1,74$, $p < 0.01$).

DISCUSSION

This study demonstrated a significant reduction in the FA values of the WM in many areas of the brain predisposed patients to delirium after the cardiac operation. However, a comparison of the FA values between the delirium group and the nondelirium group analyzing age as the nuisance covariate revealed a statistically significant change in only four clusters of the brain areas. Consequently, it seems that the majority of the brain areas which exhibited a significant decrease in the FA values of the delirium group were involved in the age-related changes in the WM.

Histological studies of postmortem brains have reported age-related alterations in the WM, such as a decline in the volume, number, and length of the myelinated fibers.[42–44] Many cross-sectional, longitudinal, and structural MRI studies showed age-related volume increases in the cerebrospinal fluid (CSF)-filled space that primarily occurred at the expense of cortical gray matter and with most showing little volume change in the WM,[19] whereas a few studies reported that there was a steady decline in the WM volume.[45,46] However, DTI studies including this study indicated age-related declines in the FA values of WM in normal healthy adults in whom volume declines were not necessarily detectable,[16–24] which may be attributable to the changes in the WM observed in the postmortem brains.[42–44]

The core features of delirium are disturbances in consciousness and attention.[1,2] The integrity of the WM in CNS is required to control consciousness and pay attention to objects. The brain states of vigilance are controlled by a system that originates in the

TABLE 3. Decreases in the FA Values of Patients With Delirium

Anatomical Regions	MNI Coordinates			*t*	
	x	*y*	*z*	Model 1[a] (*df* = 114)	Model 2[b] (*df* = 113)
Thalamus					
Left ventral anterior nucleus	−8	−6	6	4.96	3.37
Left ventral lateral nucleus	−10	−12	8	4.42	
Left pulvinar	−20	−28	12	4.31	
Left ventral posterior lateral nucleus	−16	−16	8	3.62	
Left lateral posterior nucleus	−20	−20	12	3.76	
Right anterior nucleus	6	−4	8	4.04	
Right ventral anterior nucleus	12	−6	8	3.39	
Right pulvinar	16	−32	12	4.08	
Right ventral lateral nucleus	16	−16	12	3.28	
Temporal lobe					
Left superior temporal gyrus WM	−36	−40	8	4.44	
Left middle temporal gyrus WM	−56	−36	10	3.21	
Left subgyral WM	−44	−36	−4	3.85	
Right superior temporal gyrus WM	38	−38	8	3.50	
Right subgyral WM	42	−36	−4	3.51	
Frontal lobe					
Left inferior frontal gyrus WM	−36	32	8	3.46	
Left precentral gyrus WM	−36	−4	36	3.41	
Left subgyral WM	−22	−32	34	4.86	3.46
Right subgyral WM	40	0	22	3.53	
Parietal lobe					
Left supramarginal gyrus WM	−48	−42	34	3.42	
Left precuneus WM	−20	−56	36	3.61	
Left subgyral WM	−22	−52	38	3.53	
Right subgyral WM	34	−52	32	3.23	
Limbic lobe					
Left cingulate gyrus WM	−20	−10	42	3.86	
Right cingulate gyrus WM	20	−24	36	4.75	3.47
Left anterior cingulate WM	−12	24	22	3.60	
Corpus callosum (splenium)	−6	−34	20	4.58	3.18

Notes: The FA values were compared between the two groups (patients with or without postoperative delirium) by a voxel-by-voxel analysis using the SPM2. MNI: Montreal Neurological Institute.

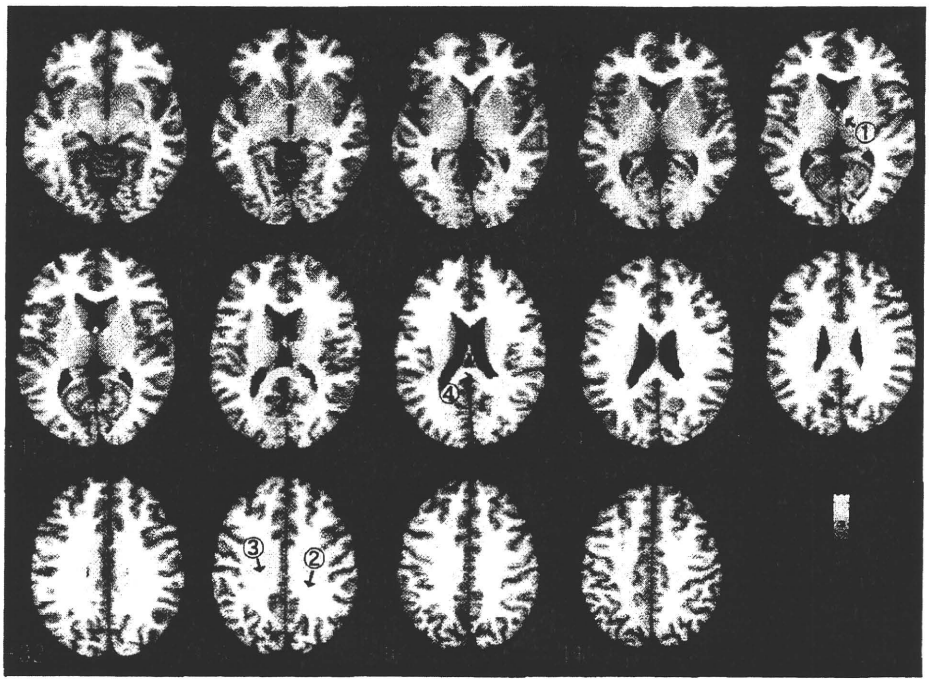
[a]In Model 1, to estimate population effects (diagnostic effects), we used a single subject condition (nondelirium [n = 97] or delirium [n = 19]) and covariate (no covariate of interest) model for the SPM analysis.

[b]In Model 2, we applied the single subject condition (nondelirium [n = 97] or delirium [n = 19]) and covariate (covariate of interest; age). For the analyses, we set the masking threshold for the FA values of 0.2 for excluding voxels containing partial volume of WM and other tissues. We used the one-tailed $p < 0.001$ (uncorrected) as a statistical threshold to search for significant differences between the groups.

brainstem and projects through synaptic relays in the thalamus to the cerebral cortex,[47,48] and neural networks composed of a number of brain areas including the cerebral cortices (e.g., posterior parietal cortex, frontal eye fields, and cingulate cortex) and subcortical areas (e.g., thalamus, striatum, and the reticular activating system) play an important role in visuospatial attention.[49–51] It is also suggested that there is widespread disruption of higher cortical function involving the several brain areas in delirium.[52] Consequently, it is likely that the alterations in the microstructure of the WM underlay a vulnerability of the patients to develop postoperative delirium in this study.

All the subjects of this study had a minimal impairment of cognitive function. A sensitive decline in the delirium group was observed in the executive functions such as the Trail Making tests and the word fluency tests, in accordance with a recent study reporting that the mildly impaired cognitive performance can be an independent risk factor for postoperative delirium.[13] The decrease in the functions with normal aging is supposed to be paralleled with the anatomical changes of the frontal lobe and its connection with other brain areas.[23,53] Moreover, the multivariate stepwise logistic analysis indicated that the lower WFTA score was an important predisposed risk factor for the postoperative delirium. It has been reported that the semantic fluency

FIGURE 3. Comparisons of FA Values Between the Delirium and Nondelirium Group by a Single Subject Condition With the Covariate (Age) Model for the SPM2



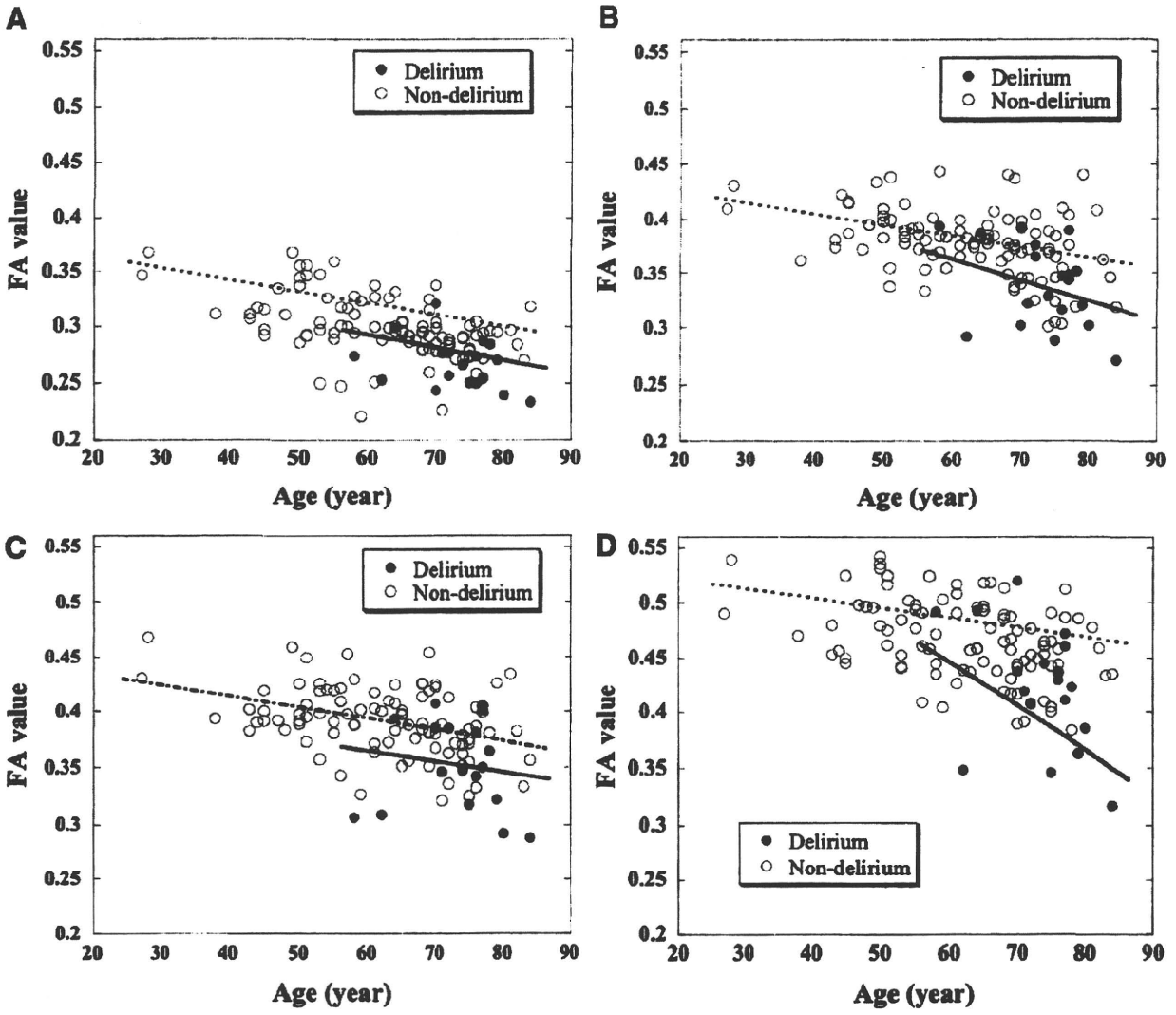
The SPM{t} values (one-tailed p <0.001, uncorrected) are displayed on the axial FA template images. A significant decrease in the FA values was observed in four clusters of the brain area. The area of maximum change in each cluster was ① the left thalamus (nucleus ventralis anterior)(the Montreal Neurological Institute (MNI) coordinates; $x = -8, y = -6, z = 6$), ② the left frontal lobe (subgyral white matter) (MNI coordinates; $x = 22. y = -32, z = 34$), ③ the right limbic lobe (cingulate gyrus white matter) (MNI coordinates; $x = 20, y = -24, z = 36$) and ④ the corpus callosum (splenium) (MNI coordinates; $x = -6, y = -34, z = 20$) (Table 3). The brain area is marked by an arrow with the number.

task such as WFTA was more useful than the letter fluency task for discriminating between healthy aging and mild dementia of the Alzheimer type.[33,54] Thus, this study suggests a similar usefulness of the word fluency tests for predicting a risk for postoperative delirium.

A number of limitations of our study ought to be mentioned. Because this study was carried out in a limited number of patients who underwent the planned cardiac operation, further examinations carried out in a larger group of subjects or with any modification to the design of the study, such as a noncardiac operation, are required to confirm and generalize the observation of this study. Secondary, although the assessment by the T1 and T2-weighed images could not find any quantitative difference between the two groups in this study (data not shown), it is likely that small and silent insults of cerebrovascular arteriosclerosis observed in the older persons interfere the FA values of the WM. Thus, the relationship between the fiber integrity and the pathological changes needs to be explored further. Another limitation is the spatial normalization of WM regions in the voxel-based analysis of FA data,[14,41] whereas many studies using the analysis have already provided an important insight into microstructural WM abnormalities in neuropsychiatric disorders.[39–41,55,56] Large variations of brain shape in older subjects might limit an ability to achieve the normalization across the subjects. The FA values in some regions surrounding the ventricles (Figs. 2 and 3) could be distorted by the misregistrations of image and underlying variation of brain shapes.

In conclusion, this study revealed that the advanced age and the cognitive decline were important predictive indicators of the postoperative delirium and suggests that the abnormalities of the microstructure in the

FIGURE 4. Scatter Plots of the FA Values With Age in Four Brain Areas



[A] The left thalamus (nucleus ventralis Anterior), [B] the left frontal lobe (subgyral white matter), [C] the right limbic lobe (cingulated gyrus white matter), and [D] the corpus callosum (splenium). The FA values of the delirium group were significantly decreased in the four brain areas (left thalamus [nucleus ventralis anterior]: $F = 11.13$, $df = 1,113$, $p < 0.01$, left frontal lobe [subgyral]: $F = 11.87$, $df = 1,113$, $p < 0.001$, right cingulate gyrus: $F = 11.94$, $df = 1,113$, $p < 0.001$, corpus callosum: $F = 10.00$, $df = 1,113$, $p < 0.01$) compared with those of the nondelirium group. The analysis was performed by ANCOVA with the age of the patients treated with as a nuisance covariate. The linear regression lines between the age (x) and the FA values (y) of each brain area for the nondelirium group (the thalamus [$y = -0.001 \times x + 0.383$, $r = 0.488$, $df = 95$, $p < 0.0001$], the frontal lobe [$y = -0.001 \times x + 0.352$, $r = 0.394$, $df = 95$, $p < 0.0001$], the cingulate gyrus [$y = -0.001 \times x + 0.465$, $r = 0.376$, $df = 95$, $p < 0.0001$] and the corpus callosum [$y = -0.002 \times x + 0.465$, $r = 0.398$, $df = 95$, $p < 0.0001$]) and the delirium group (the thalamus [$y = -0.001 \times x + 0.352$, $r = 0.346$, $df = 17$, $p = 0.147$], the frontal lobe [$y = -0.002 \times x + 0.51$, $r = 0.396$, $df = 17$, $p = 0.0936$], the cingulate gyrus [$y = -0.001 \times x + 0.394$, $r = 0.089$, $df = 17$, $p = 0.716$], and the corpus callosum [$y = -0.004 \times x + 0.685$, $r = 0.431$, $df = 17$, $p = 0.0656$]) are indicated by the dotted lines and solid lines, respectively.

deep WMs and thalamus are predisposed in the patients with delirium and putatively account for the underlying mechanism of age-related vulnerability to delirium. On the other hand, the FA values in the four brain areas such as left ventral anterior nucleus of the thalamus may be affected by factors other than aging,

supported by the additional analysis in the subgroup of the subjects older than 60 years indicating that the decreased FA values of the brain areas in the delirious patients were also statistically significant. Thus, further DTI studies to clarify factors other than aging affecting the microstructure of the WM, e.g., arteriosclerosis, can provide a new insight into the brain condition vulnerable to delirium.

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