医療観察法の判断構造

触法精神障害者の責任能力と医療的処遇はそれぞれ刑事司法と医療という異なる次元にある．責任無能力の認定が医療の門に直結するわけではない．しかしこの点は誤解されやすく，医療に馴染む者は責任無能力者，馴染まない者は完全責任能力であるという転倒した認識さえみられる．問題はリンクの仕方，言い換えれば刑事手続から医療へのダイバージョンの経路にある．

従来の制度では，精神障害者またはその疑いのある被疑者，被告人について不起訴処分などがなされた場合，検察官は精神保健福祉法に基づく通報を行う．この段階で患者の処遇は刑事司法の手を離れ，医療的判断のもとに置かれる．

それでは医療観察法ではどうであろうか．医療観察法33条は検察官が地方裁判所への申立てを行わなければならない場合の要件を次のように規定する．対象行為(殺人，放火，強盗，強姦，強制わいせつ，傷害)を行ったこと，心神喪失者もしくは心神耗弱者であることを認めて公訴を提起しない処分をしたか，心神喪失者として無罪の確定裁判または心神耗弱者として刑を減軽する確定裁判(執行すべき刑期がある者を除く)を受けたことである．

つまり，医療観察法の運用においては医療処遇と責任能力がリンクしている．言い換えれば責任主義が少なくとも建前上は堅持されている．これについて具体的にみると，上述のように検察官の申立てには「公訴を提起しない処分」つまり不起訴処分と確定裁判後という２つの場合がある．大多数は前者と予想され，実際，施行から１年間の統計[5]では申立ての合計355人中88.5％が不起訴処分，11.3％が確定裁判での執行猶予の事例であり，無罪判決を経た事例はわずか１人である．

この傾向は従来と変わらない検察の方式を反映している．近年，心神喪失者・心神耗弱者と認定される者の９割弱は不起訴処分とされ，裁判の段階でこれらが認定される割合は非常に低く，とくに心神喪失の認定は年間１～２例に過ぎない．刑事訴訟法は「犯人の性格，年齢及び境遇，犯罪の軽重及び情状並びに犯罪後の情況により訴追を必要としないときは，公訴を提起しないことができる」と定めている．いわゆる起訴便宜主義であり，これに基づいて裁判以前に検察のレベルで責任能力の「前倒し判断」[6]がなされ，処分が決定されている．裁判で責任能力が争われる事例はあくまで少数の“上澄み”であるに過ぎない．日本の刑事司法は責任主義を維持しているが，それは同時に起訴便宜主義と一体となっている．

医療観察法においても責任能力に関する検察の前倒し判断の構造は変わらない．むろん裁判所にも責任能力をチェックする機能は保証されている．40条１項では，裁判所は決定をもって申立てを却下しなければならない事由として「心神喪失者及び心神耗弱者のいずれでもないと認める場合」をあげている．実際，すでにそのような却下の事例があると聞く．しかしこれは裁判所の審判の主目的ではない．

このような法の趣旨は申立てを受けて行われる鑑定つまり医療観察法鑑定の性格にも現れている．すなわち，裁判所は「精神障害者であるか否か及び対象行為を行った際の精神障害を改善し，これに伴って同様の行為を行うことなく，社会に復帰することを促進するためにこの法律による医療を受けさせる必要があるか否か」について医師に鑑定を命じなければならない(37条)．さらに，現場で準拠されている厚生労働科学研究班の『鑑定ガイドライン』[7]を参照すると，鑑定の目的は，対象者が精神障害者であるか否かと医療観察法による医療の必要性である．刑事訴訟手続における鑑定とは異なり，医療観察法鑑定は「対象者の医療観察法における医療必要性についての意見を述べるもの」と説明されている．すなわち，医療観察法鑑定は医療の必要性と当該行為時の責任能力を一体として評価する役割をもたない．裁判所の目配りが十分でない場合，責任能力は医療観察法の入り口で決定済みということになる．検察官が申立ての資料として嘱託する鑑定を“申立て前鑑定”と呼ぶと，医療観察法のもとでの判断構造は図１のように二階建てとなる．

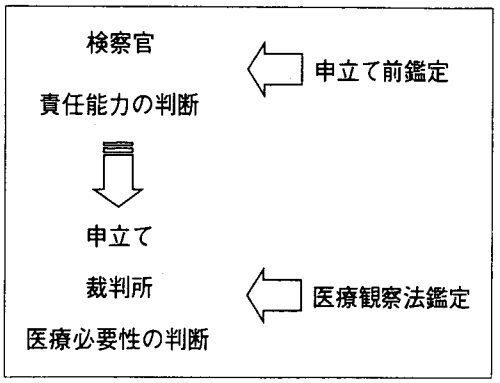

図1　医療観察法の判断構造

触法精神障害者のこれから

医療観察法を軸とする触法精神障害者の医療に今後どのような展開が予想されるであろうか．この場合，医療環境ばかりでなく司法環境つまり刑事政策や裁判制度の変化も無視できない．また，医療の提供は医療観察法に限られるわけではなく，刑罰を科せられた場合は矯正施設で，また「重大な」他害行為に当たらない触法行為の場合は精神保健福祉法のもとでの治療の対象となる．つねに全体を捉える視点から検討されなければならない．

まず，要をなす医療観察法の性格を見定める必要がある．施行から1年半余りが経過した現時点で医療・福祉関連法としての性格をより鮮明にしつつあるように見受けられる．対象者への濃厚な医療と社会復帰への援助が主眼とされ，社会の安全確保は従属的な要素とされている．これは法案が審議される過程で「再び対象行為を行うおそれ」という文言が削除されたことによってすでに方向づけられていた．

法のこのような性格はドイツの改善保安処分と比較すると明らかとなる．主な処分である精神科病院収容は「人が責任無能力もしくは限定責任能力の状態において違法行為を行ったとき，裁判所は，行為者およびその行為の全体的評価に基づき，その者の状態の結果として著しい違法行為が予測され，そのため公共に対して危険であることが明らかであれば，精神科病院への収容を命じる」というもので，公共への危険性の要件が条文に明記されている．また，ドイツの制度では責任能力の認定と改善保安処分の言い渡しがともに刑事裁判で行われ，上述の医療観察法における判断の二層構造とは異なっている．

ただし，医療観察法には本質的な曖昧さがつきまとう．精神障害の改善と社会復帰を目的に掲げる一方で，殺人などの「重大な」他害行為を行ったことを要件としている．この点ではかつての法務省の「保安処分制度(刑事局案)」を明らかに踏襲しており，疾患の重症度ではなく社会的危険性に照準を合わせている．また，裁判所が行うのは“裁判”ではなく，裁判官と精神保健審判員が同等の資格をもつ“審判”であるが，裁判所は対象行為の存否や責任能力に関する刑事司法レベルの判断もなしうる．さらに保護観察所という矯正機関が関与するが，その役割は「適当な接触を保つ」「生活の状況を見守る」という控えめなものである．医療観察法のユニークな性格を筆者は刑事司法と医療の折衷モデルと呼んでいる[8]．

さて，医療観察法を医療・福祉的な方向へ純化していくことは，それ自体は一つの選択として是認してよい．しかし，結果として法の守備範囲から外れる事例が生じることを忘れるべきではない．とくに問題となるのは心神耗弱者の扱いである．対象行為を行い，心神耗弱と認定されると，起訴されるか，不起訴処分を経て医療観察法の申立てがなされるか，2通りが考えられる．通り魔殺人のように地域住民の不安や被害者側の処罰感情が著しく強い事件の場合，統合失調症などで医療の必要性が明白であっても，検察官は社会的配慮からこれを起訴する可能性が高い．そして，今日の厳罰化の流れのもとで，重い刑が求刑されるであろう．刑事裁判は医療観察法の要否を決定する場ではないので，医療の必要性を理由として刑が減軽される見込みもない．触法精神障害者の処遇は，一方では医療観察法のもとでの手厚いケア，他方では重い刑事罰という相反する方向に二極化するのではないだろうか．今後の推移を注意深く見守りたい．

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専門医制度委員会企画

第16回専門医制度委員会企画

法と精神医学

中谷 陽二（筑波大学大学院人間総合科学研究科ヒューマン・ケア科学専攻）

はじめに

精神科医は臨床の場でさまざまな法律問題に関わる．最も身近な精神保健福祉法の他にも，裁判所や検察庁から依頼される鑑定，心神喪失等医療観察法の鑑定，成年後見のための鑑定書・診断書の作成などに従事する機会がある．臨床医は経験則に頼りがちであるが，関連する主な法制度については正確な知識を持つことが望ましい．ここでは刑事精神鑑定，医療観察法，成年後見を主に解説し，精神保健福祉法やその他の問題は腕試し問題で補うことにする．

Ⅰ．精神鑑定

一般に「鑑定」とは刑事訴訟法，民事訴訟法で定められたもので，特別の学識経験を持つ者が行う法則や事実についての判断や意見である．精神鑑定は広い意味で診断行為であるが，法律の手続に組み込まれ，法的判断に資することを一義的な目的とする．措置入院の指定医診察も「鑑定」と呼ぶ習慣があるが，法律の枠組が全く異なるので混同されてはならない（精神保健福祉法の条文には“鑑定”という語は存在しない）．

触法精神障害者を対象とする精神鑑定の種類を表1に示す．起訴前鑑定は起訴，不起訴の決定資料として検察官が医師に委託するもので，裁判所の令状で鑑定留置（身柄の拘束）がなされる本鑑定（嘱託鑑定）と，勾留期間内に本人の同意を得て行われる簡易鑑定（精神衛生診断）の2種がある．起訴された被告人については裁判官の職権で公判鑑定が行われる．簡易鑑定は文字通り“簡易”な鑑定であるが，検察官の判断を左右するという意味で重大な法的結果を招き得るし，医療観察法の申立てを検察官が行う場合の資料ともされるので，疎かにできない．

何を鑑定すべきかは“鑑定事項”として委託者から与えられる．たいていは「犯行時および現在の精神状態」であるが，知能程度，酩酊の程度など個別の課題が要求されることもある．後述する責任能力について鑑定書でどこまで言及すべきかが問題になる．起訴前鑑定ではこれが鑑定事項に含まれることが多く，公判鑑定でも同様の場合がある．鑑定事項に示されていない場合でも，証人尋問で責任能力について問われることが通例である．

鑑定書の提出後，法廷に召喚されて証人として尋問を受けることを予期すべきである．起訴前鑑定でも，鑑定書が裁判の証拠として扱われると召喚される可能性がある．鑑定人が意図して偽るこ

表1 触法精神障害者に関わる精神鑑定

起訴前精神鑑定
簡易鑑定（精神衛生診断）
―裁判所の許可不要、本人の同意
本鑑定（嘱託鑑定）
―裁判所の許可による鑑定留置
公判鑑定
―裁判所の権限
医療観察法鑑定
―医療観察法の対象者

とは考えにくいが，偽証罪があることを念頭に置いた方がよい．

II．責任能力

犯罪をおかした精神障害者について刑罰を特別に軽くする慣行は洋の東西を問わず古来から存在した．フランスでは1810年刑法のデマンス(démence)の規定，イギリスでは1843年のマクノートン準則，ドイツでは1871年刑法の「自由な意思決定の欠如」が近代の責任能力規定の基礎をなす．責任とは違法な行為について行為者を道義的に非難しうることで，「責任なければ刑罰なし」という責任主義は近代刑法の基本原則とされる．

日本の刑法第39条は「心神喪失者の行為は，罰しない．心神耗弱者の行為は，その刑を減軽する．」と定めている．責任無能力者を指す法律上の文言が「心神喪失者」，限定責任能力者が「心神耗弱者」である．明治時代に法律が整備される過程で，民法の禁治産，準禁治産での心神喪失，心神耗弱の語が刑法にも取り入れられた．民法でいう心神喪失は精神障害により自己の利害得失に関する判断能力を欠くことであり，是非善悪を弁識する能力である刑法上の心神喪失とは異なる．大審院判決（1931年）は心神喪失を「精神の障礙に因り事物の理非善悪を弁識する能力なく又は此の弁識に従て行動する能力なき状態」，心神耗弱をこれらの能力の「著しく減退せる状態」と定義した．

このように責任能力は〈精神障害〉〈是非の弁識能力〉〈行動の制御能力〉から構成され，精神障害の有無や性質は“生物学的要素”，弁識と制御の能力の程度は“心理学的要素”と呼ばれる(誤解されやすい用語であるが慣用されている)．ドイツや日本ではこれら2つの要素を総合して判断する“混合法”が採用されている．

心神喪失と心神耗弱は法律概念であり，最高裁判所の判決もこれについての判断は裁判所に委ねられると明言している．そうすると鑑定人の任務は法的判断のための医学的資料を提供するにとどまることになる．しかし責任能力に関して踏み込んだ意見が鑑定人に求められるのが実情である．筆者は便宜上，「鑑定人の立場での参考意見」と断った上で責任能力についても鑑定書に記載することにしている．

III．医療観察法

正式名称は「心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律」である．措置入院では触法精神障害者への対応が不十分であることなどを理由に2005年7月から施行されている．重大な他害行為（殺人，放火，強盗，強姦，強制わいせつ，傷害）を行い，心神喪失または心神耗弱を理由に不起訴処分か裁判で無罪または刑の減軽（刑期のあるものを除く）を受けた者について検察官は地方裁判所へ申立てを行う（傷害以外については未遂も含む)．

裁判所は2ヶ月を超えない鑑定入院を行う（1ヶ月以内の延長可能)．鑑定医は鑑定結果に本法による医療の必要性に関する意見を付す．厚生労働科学研究班の『鑑定ガイドライン』によれば，医療観察法鑑定は，①対象者が精神障害者であるか否か，②医療観察法の医療必要性，を明らかにする．医療必要性は疾病性，治療反応性，社会復帰要因のいずれもが一定水準を上回ることで認定されるとしている．

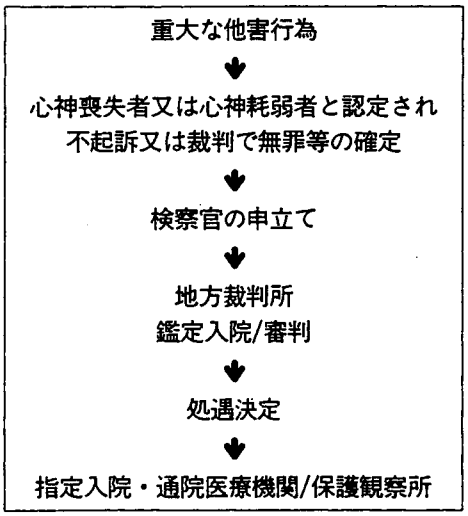

図1　医療観察法の概要

表2 成年後見制度の概要

類型	対象者	援助者	診断
後見	精神上の障害により事理を弁識する能力を欠く常況にある者	成年後見人	鑑定
保佐	上記の能力が著しく不十分な者	保佐人	鑑定
補助	上記の能力が不十分で後見または保佐の要件に当たらない者	補助人	診断書*
任意後見	判断能力低下に備えて予め契約	任意後見人	診断書*

* 必要に応じて鑑定

審判は裁判官，精神保健審判員各1名の合議で，必要に応じ精神保健参与員の意見を聴く．鑑定結果に基づいて処遇の要否と内容を決定する．すなわち，①対象行為を行った際の精神障害を改善し，これに伴って同様の行為を行うことなく，社会に復帰することを促進するため，入院をさせてこの法律による医療を受けさせる必要があると認める場合：医療のため入院させる決定．②この法律による医療を受けさせる必要が認められるが①に当たらない場合：入院によらない医療を受けさせる決定．③上記のいずれにも当たらない場合：この法律による医療を行わない決定．④申立てが不適法と認める場合：申立ての却下．

医療は指定入院医療機関及び指定通院医療機関で行う．入院によらない場合，対象者は精神保健観察に付され，保護観察所の社会復帰調整官が必要な指導などを講ずる．退院または入院継続は医療機関の管理者が保護観察所長の意見を付して，処遇の終了と再入院は保護観察所の長が医療機関の管理者と協議の上，裁判所に申立て，裁判所が決定を行う．

医療観察法の制定に伴って設けられた医師の資格，役職は精神保健判定医と精神保健審判員である．厚生労働大臣は政令によって精神保健審判員の職務を行うのに必要な学識経験を有する医師（精神保健判定医）の名簿を最高裁判所に送付する．地方裁判所はこの名簿に記載された者のうち毎年あらかじめ選任した者の中から処遇事件ごとに精神保健審判員を任命する．審判員の主な任務は裁判官とともに合議体を開き，評議で意見を述べることであり，精神医学の専門家として裁判官と対等の立場で決定に与る重要な役割を負う．

IV. 成年後見制度

民法では「心神喪失の常況にある者」について家庭裁判所が禁治産を宣告することができ，禁治産者は後見に付して，禁治産者の行為は取り消すことをできると規定した．また「心神耗弱者及び浪費者」については準禁治産者として保佐人を付することをできるとした．社会の高齢化に押されて禁治産宣告が急増した結果，画一性，取り消さない限り禁治産者であり続けること，本人に告知されないこと，戸籍への記載，親族間の紛争の道具として濫用されやすいことなど，種々の弊害が認識されるようになった．

このような背景のもとで2000年4月から面目を一新した成年後見制度が施行されている．法改正はノーマライゼーションの理念に沿い，自己決定の尊重と残存能力の活用や柔軟かつ弾力的な利用しやすさを目指した．表2に示すように，旧制度での禁治産，準禁治産の2本立てから，後見，保佐，補助の3類型（法定後見）に加えて任意後見が設けられ，選択肢が増えている．対象者の能力障害の程度に応じて，自己決定の範囲と援助者に委ねられる権限（同意権，取消権，代理権など）の範囲がきめ細かく定められている．

申立ては本人，配偶者，4親等内の親族等であり，家裁調査官による調査を経て，後見と保佐では原則として鑑定が，補助と任意後見では診断書が必要である．家裁での審判を経て告知され，開

始される．鑑定書と診断書の作成のために最高裁判所事務総局から「手引」が発行されている．成年後見の対象者の多数を高齢者が占めるが，知的障害及び統合失調症その他の精神障害で判断能力の不十分な成年者ももちろん対象となる．

文　献

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2) 最高裁判所事務総局：新しい成年後見制度における鑑定書作成の手引．2000

3) 最高裁判所事務総局：新しい成年後見制度における診断書作成の手引．2000

4)「心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律」（医療観察法）鑑定ガイドライン．厚生労働科学研究班研究費補助金こころの健康科学研究事業「触法行為を行った精神障害者の精神医学的評価，治療，社会復帰等に関する研究」成果報告，2005

腕試し問題

問1．精神衛生法(1950年)と精神保健福祉法(1995年)の「法律の目的」の主な相違点は何か．

問2．次の事例で，主治医が入院を勧めたところ，患者がA，Bの2通りの反応をしたと想定する．それぞれについて選択肢の中から適当なものを選び，その理由を説明せよ．

33歳の主婦．妄想型統合失調症．2度の入院歴があり，現在まで同じ医師が主治医を務めている．6か月前に寛解状態で退院した．2か月前から服薬が不規則となり，興奮や自傷はないが，不眠がちで，話しかけても上の空となった．病状の悪化を心配した夫に付き添われて来院した．診察には応じるが，表情が硬く，緊張がうかがわれる．質問にはおおむね答えるが，時に幻聴に注意を奪われ，小声の独語を発する．夫は入院を希望している．

【A】主治医が「しばらく入院して治療しましょう」と告げたところ，患者はうなづいて承諾の意思表示をした．理由を問うと，「自分は病気ではないけれど，入院しなさいという(幻覚の)声が聞こえるから」と答えた．入院の目的を説明したが，態度は変わらなかった．

①任意入院とする．　②医療保護入院とする．

【B】主治医が「しばらく入院して治療しましょう」と告げたところ，患者は首を横に振って拒否の意思表示をした．理由を問うと，「先生が言われることはわかりますが，育児から手が離せませんから」と，生活上の理由をあげた．さらに説得したが，態度は変わらなかった．

①入院は行わない．　②医療保護入院とする．

問3．日本の刑法は精神障害者の責任能力をどのように規定しているか．

問4．刑事事件の被疑者・被告人について行われる精神鑑定の種類と手続を説明せよ．

問5．医療観察法において検察官が地方裁判所への申立てを行わなければならない場合の要件は何か．

問6．医療観察法は申し立てられた対象者について裁判所は医師に鑑定を命じ，鑑定医は「この法律による入院による医療の必要性に関する意見」を鑑定結果に付さなければならないと定めている．次の事例ではどのような意見が考えられるか．

26歳の男性．会社員の家庭で養育され，内気な性格で非行はなかった．中学の終わり頃から腋臭を気にした．高校を卒業し，親元から離れて予備校に通った．浪人中も腋臭が気になった．2年後に大学に入学したが，友人たちが何か隠しているように感じ，通学が苦痛になり，退学した．常に疎外感を抱き，単身で職を転々とした．家族との接触も避けるようになった．対象行為の半年前，「隣人からマインドコントロールされる」という体験があり，隣家の窓に石を投げた．「車を運転していると前方の車がわざと急ブレーキをかける」と感じ，護身用ナイフを持ち歩くようになった．精神科治療歴はない．対象行為は，電車内でいきなり無関係の男性にナイフで切りつけ，全治2週間の傷害を負わせたもの．警察で動機を問われると，「理由は被害者に聞けばわかる」な

どと奇妙な発言に終始した．起訴前鑑定では被害関係妄想，幻聴，被影響体験，性格変化を症状とする妄想型統合失調症と診断され，不起訴処分とされて医療観察法の申立てがなされた．医療観察法鑑定では，陰気，寡黙で，差しさわりのない会話には応じるが，質問が妄想体験や対象行為に触れると急に硬い表情になって黙りこんだ．

問7．成年後見制度にはどのような類型があるか．それぞれどのような対象者に適用されるか．

問8．次はアルツハイマー病の事例である．(1)～(5)に当てはまる言葉は何か．

5年程前から物忘れがひどくなり，勤務先の直属の部下を見ても誰かわからなくなるなど，次第に社会生活を送ることができなくなった．日常生活においても，家族の判別がつかなくなり，その症状は重くなる一方で回復の見込みはなく，2年前から入院している．ある日，本人の弟が突然事故死し，本人が弟の財産を相続することになった．弟には負債しか残されておらず，困った本人の妻が(1)のために，(2)の審判を申し立てた．家庭裁判所の審理を経て，本人について(3)が開始され，夫の財産管理や身上監護をこれまで事実上担ってきた妻が(4)に選任され，妻は(5)の手続をした．（最高裁判所「成年後見関係事件の概況」から改変して引用）

問9．中毒者を診断したときの医師の届出義務は「麻薬及び向精神薬取締法」と「覚せい剤取締法」でどのように規定されているか．

問10．刑法及び精神保健福祉法は守秘義務をどのように定めているか．

【第15回専門医制度委員会企画・腕試し問題解答】

問1：4)　問4：5)　問7：3)　問10：1)，5)
問2：1)，5)　問5：2)，3)　問8：4)，5)
問3：5)　問6：1)，5)　問9：2)

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Multivariate voxel-based morphometry successfully differentiates schizophrenia patients from healthy controls

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Currently available laboratory procedures might provide additional information to psychiatric diagnostic systems for more valid classifications of mental disorders. To identify the correlative pattern of gray matter distribution that best discriminates schizophrenia patients from healthy subjects, we applied discriminant function analysis techniques using the multivariate linear model and the voxel-based morphometry. The first analysis was conducted to obtain a statistical model that classified 30 male healthy subjects and 30 male schizophrenia patients diagnosed according to current operational criteria. The second analysis was performed to prospectively validate the statistical model by successfully classifying a new cohort that consisted of 16 male healthy subjects and 16 male schizophrenia patients. Inferences about the structural relevance of the gray matter distribution could be made if the individual profile of pattern expression could be linked to the specific diagnosis of each subject. The result was that 90% of the subjects were correctly classified by the eigenimage, and the Jackknife approach revealed well above chance accuracy. The pattern of the eigenimage was characterized by positive loadings indicating gray matter decline in the patients in the lateral and medial prefrontal regions, insula, lateral temporal regions, medial temporal structures, and thalamus as well as the negative loadings reflecting gray matter increase in the patients in the putamen and cerebellum. When the eigenimage derived from the original cohort was applied to classify data from the second cohort, it correctly assigned more than 80% of the healthy subjects and schizophrenia patients. These findings suggest that the characteristic distribution of gray matter changes may be of diagnostic value for schizophrenia.
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Introduction

Current operational diagnostic systems for major psychiatric disorders such as schizophrenia are based solely on clinical manifestations and associated psycho-social impairments (World Health Organization, 1993; American Psychiatric Association, 1994). It has been suggested that multiple laboratory tests might permit a more refined classification of mental disorders characterized by improved homogeneity and greater etiologic validity (Carter et al., 2002; Murray et al., 1992; Sponheim et al., 2001, 2003). It may be possible for currently available laboratory procedures to provide additional information to psychiatric diagnostic systems for more valid classifications, but little progress has been made in the clinical application of biological indices as a diagnostic tool.

Converging evidence has revealed that subtle but significant structural changes are observed principally in fronto-temporolimbic-paralimbic regions in schizophrenia (Shenton et al., 2001; Tien et al., 1996; Wright et al., 1999). Because the anatomy of the brain is stable relative to clinical manifestations and functional brain measures, structural neuroimaging may be a useful tool for the clinical diagnosis of schizophrenia. Suddath et al. (1990) found that visual inspection of the MRI scans of monozygotic twins discordant for schizophrenia allowed identification of the affected twin in 12 of the 15 pairs. Another study showed that a combination of 10 anatomical variables on MRI scans enabled reliable classification of 76% of male schizophrenia patients and 79% of male controls (Leonard et al., 1999). Our previous MRI study with discriminant function analysis using 14 anatomical measures showed correct classification of 80% of the male and 78% of the female schizophrenia patients, and 80% of the male and 86% of the female controls (Nakamura et al., 2004). These results suggest clinical applicability of structural neuroimaging data to a future diagnostic system for schizophrenia. The limited number of

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morphological parameters, however, has compromised the significance of the previous methods.

Voxel-based analysis based on the stereotactic coordinates provides a whole-brain and unbiased technique for characterizing regional cerebral function and structure. The multivariate linear model (MLM) has recently been proposed to characterize the functional brain response as a global pattern in the brain (Kherif et al., 2002; Worsley et al., 1997). The MLM method uses canonical variates analysis (CVA) (Friston et al., 1995) of corrected least-squares estimators, but unlike partial least squares (PLS) (McIntosh et al., 1996), the inferences depend on parametric multivariate linear models rather than simulations. The MLM is an extension of the CVA and the PLS to deal with the limitation of the CVA and the PLS (Worsley et al., 1997). The MLM takes into account the spatial covariance between the voxels and provides a formal test of the number of components based on Gaussian random field theory. Our MLM analysis, similar to the discriminant function analysis (Kherif et al., 2003), can identify the models of variation (i.e., eigenimage) that best represent inter-subject variability. An eigenimage and subject scores are obtained by MLM analysis of certain original data. Because the eigenimage can be used as a predictor within the separate test data for a replication, prospective classification is made based on the subject scores of test data. This method has been reported to be useful for characterizing differences in trait-related brain activity during working memory task by showing that the eigenimage perfectly separated all schizophrenia patient scans from those of the comparison subjects and successfully classified prospectively examined independent group of data (Meyer-Lindenberg et al., 2001). Application of the MLM to voxel-based morphometry (VBM) (Ashburner and Friston, 2000) would enable us to capture and explain the interrelationship between the voxel-wise MRI data and a set of predictors, such as a clinical diagnosis of subjects, in the spatial pattern of tissue distribution. Thus, this procedure would provide a diagnostic method, rather than focusing on producing maps of significant structural differences, to show the probability that a subject falls into one of a number of diagnostic categories. To our knowledge, MLM analysis with the VBM has never been applied to distinguish schizophrenia patients from healthy subjects.

In the present study, we hypothesized that the characteristic distribution of regional gray matter changes in schizophrenia patients would have some power to discriminate them from healthy subjects. The question at issue is the degree to which a statistical model with factors associated with brain structural changes in schizophrenia correctly classifies subjects into groups according to the current diagnostic system. The analysis design of the present study was twofold: the first analysis was conducted to produce a statistical model to classify subjects according to the current diagnostic systems, and the second analysis was performed to prospectively validate the statistical model by classifying a new cohort.

Subjects and methods

Subjects

Subjects were randomly assigned to two independent groups. The first group consisted of 60 subjects comprising 30 schizophrenia patients and 30 healthy subjects. The second group for the prospective validation consisted of 32 subjects, 16 with schizophrenia and 16 who were healthy. All subjects were male, right-handed, and over 18 years and under 40 years old. Demographic and clinical data of the subjects are shown in Table 1.

Table 1
Demographic and clinical characteristics of subjects

a. Original study

Variable	Schizophrenia	Control
	Male (n=30)	Male (n=30)
	Mean (SD)	Mean (SD)
Age (years)	24.7 (4.4)	25.4 (4.4)
Height (cm)	170.2 (5.1)	171.9 (3.5)
Weight (kg)	66.3 (13.6)	64.0 (8.3)
Education (years)	13.3 (1.9)*	15.6 (1.9)
Parental education (years)	12.1 (1.8)	12.7 (2.0)
Age of onset of illness (years)	21.1 (4.3)	
Duration of illness (years)	4.0 (4.7)	
Medication (mg/day)[a]	8.7 (8.4)	
SANS summary score (0–25)[b]	11.6 (4.4)	
SAPS summary score (0–20)[b]	5.2 (3.8)	
BPRS total score (18–126)[b]	35.1 (15.0)	

b. Variation study

Variable	Schizophrenia	Control
	Male (n=16)	Male (n=16)
	Mean (SD)	Mean (SD)
Age (years)	28.6 (5.2)	24.0 (5.1)
Height (cm)	170.7 (4.3)	172.6 (4.4)
Weight (kg)	62.8 (11.9)	63.5 (6.5)
Education (years)	14.1 (1.6)*	16.4 (1.6)
Parental education (years)	12.5 (2.1)	13.1 (1.6)
Age of onset of illness (years)	23.1 (4.7)	
Duration of illness (years)	5.1 (4.8)	
Medication (mg/day)[a]	12.1 (7.4)	
SANS summary score (0–25)[b]	11.3 (4.9)	
SAPS summary score (0–20)[b]	6.7 (4.6)	
BPRS total score (18–126)[b]	34.9 (13.6)	

SANS, Scale for scale for the Assessment of Negative Symptoms.
SAPS, Scale for the Assessment of Positive Symptoms.
BPRS, Brief Psychiatric Rating Scale.
*$p<0.05$ compared with control (two-tailed t test).
[a] Haloperidol equivalent dose.
[b] Possible range.

The patients were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. Each patient underwent a Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001). Two experienced psychiatrists (T.T. and M.S.) reached a consensus diagnosis of schizophrenia according to the DSM-VI (American Psychiatric Association, 1994) as well as the ICD-10 for research (World Health Organization, 1993) on the basis of the SCID and all other sources of clinical data. Schizophrenia patients in a relatively early stage of their illness were included. All patients were physically healthy at the time of the study, and none had a history of head trauma, serious medical or surgical illness, or substance abuse disorder. All patients were being treated with antipsychotic drugs at the time of the scan. Nine of the 30 patients in the first group and six of the 16 patients in the second group were under atypical antipsychotic medication, and remaining patients were receiving typical antipsychotics. There were no significant differences between the first and second patient cohorts in age at the time of the scan, age at the onset of the initial psychotic episode, duration

of illness, or haloperidol equivalent dose. At the time of the study, their mean (SD) summary scores on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b) and mean total scores on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) were 11.2 (4.8), 5.7 (4.1), and 35.0 (14.3), respectively. There were no significant differences in clinical profile between the two patient groups (Table 1).

The control subjects were healthy volunteers recruited from hospital staffs ($n=15$), medical or pharmaceutical students ($n=10$), and candidates from the community ($n=21$). All control subjects were given the Minnesota Multiphasic Personality Inventory, and candidates were excluded if they had any abnormal profiles (i.e., individual score exceeded the 70 percentile). There were no significant between-group differences in age or height. Although the control subjects had a significantly higher educational achievement level than the patients, parental education did not differ between the groups. Candidates were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. After the purpose and procedures of the present study were fully explained, individual written informed consent was obtained from each of the subjects, and the details were filed in their clinical records. The Committee on Medical Ethics of Toyama University School of Medicine approved this study.

MRI acquisition and image analysis

The subjects underwent brain MRI scans using a Siemens 1.5 T Magnetom Vision system (Siemens Medical System Inc., Erlangen, Germany). A three-dimensional gradient-echo sequence (fast low-angle shot, FLASH) yielding 160–180 contiguous slices 1.0 mm thick in the sagittal plane was used for image analysis. Imaging parameters were: TE=5 ms; TR=24 ms; flip angle=40°; field of view=256 mm; matrix size=256×192; voxel size=1×1×1 mm^3.

Image analysis was performed with statistical parametric mapping (SPM) 99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 5.3 (Mathworks Inc., Sherborn, MA, USA). Image processing and analysis of the standard VBM (Good et al., 2001a) were performed according to the methodological description of Ashburner and Friston (2000). The spatial normalization involved transforming MRI images of all the subjects to a template that approximated the stereotactic space of Talairach and Tournoux (1988). The spatially normalized images were resliced to a final voxel size of 1×1×1 mm^3 and partitioned into gray matter, white matter, cerebrospinal fluid, and other compartments. Modulated segments of gray matter were smoothed with a 12-mm full-width at half maximum (FWHM) isotropic Gaussian kernel. Each voxel in the smoothed image contains the average concentration of gray matter from around the voxel (i.e., gray matter concentration). According to the central limit theorem, the smoothing procedure has the advantage of rendering the data more normally distributed and of increasing the validity of parametric voxel-by-voxel statistical analysis.

Statistical analysis by using SPM and MLM

In the first study, the statistical evaluation comparing schizophrenia patients and healthy controls in the first group was performed by an analysis of covariance (AnCova) model for global normalization with overall grand mean scaling. This statistical option normalizes the segmented brain images to the same total amount of gray matter, while preserving regional differences in gray matter volume.

Next, the patterns of gray matter distribution that differed most between the patients and healthy controls in the first group were extracted with MLM software (MMtoolbox, SHFJ-CEA, Orsay, France, http://www.madic.org/download/MMTBx/). The general scheme of this method is summarized in Fig. 1. The MLM method is based on singular value decomposition of the matrix Z, where Y are the data, X is the linear model, and Σ represents the temporal covariance matrix of the data (Worsley et al., 1997).

$$Z = (X'\Sigma X)^{-1/2} X'Y.$$

As there is no temporal covariance for VBM data, the matrix of present method is in fact an orthonormalized PLS in which Σ is identity therefore the matrix $X'\Sigma X$ is simplified to $X'X$. By this method, one first computed a normalized correlation between the data and a set of regressors that were contained in the design matrix. This correlation matrix was then decomposed in an "eigenimage" that best represents the variance in the correlation. Since the MLM operates on voxel-by-voxel correlation matrices, the extracted eigenimage reflected patterns of correlated gray matter concentration. The method provides an assessment of the variance explained by a given pattern, as well as a test of significance based on the MLM. The test for a global effect using S is an average of the voxel F statistics (i.e., F_i) across voxels.

$$S = \sum_{i=1}^{N} F_i / N.$$

The resultant patterns for each voxel had a positive or negative value depending on how much the gray matter concentration of this voxel contributed to the given pattern. The expression of the pattern (i.e., inner product) for every given scan was calculated as a scalar with a positive or negative coefficient. Inferences about the structural relevance of the gray matter concentration patterns were made if the individual pattern expression was linked to the specific diagnosis of the subject.

We used the following formula for the weighted mean to calculate a threshold where $\bar{X}_1$ is the mean expression value for group 1 and $\bar{X}_2$ is that for group 2, and SD_1 and SD_2 are the group standard deviations:

$$\frac{\bar{X}_1 SD_2 + \bar{X}_2 SD_1}{SD_1 + SD_2}$$

This was a simple method, which would assign all samples as belonging to one of the two groups depending on whether the coordinate fell above or below the threshold (Culhane et al., 2002).

A conservative measure to validate present discrimination method can be achieved using the Jackknife approach (Calder et al., 2001). The eigenimage was calculated by leaving one subject out which was then used to calculate the expression value.

In the second study, we tested whether the pattern of gray matter concentration obtained in the first group could be used prospectively to determine whether the disease was present. The

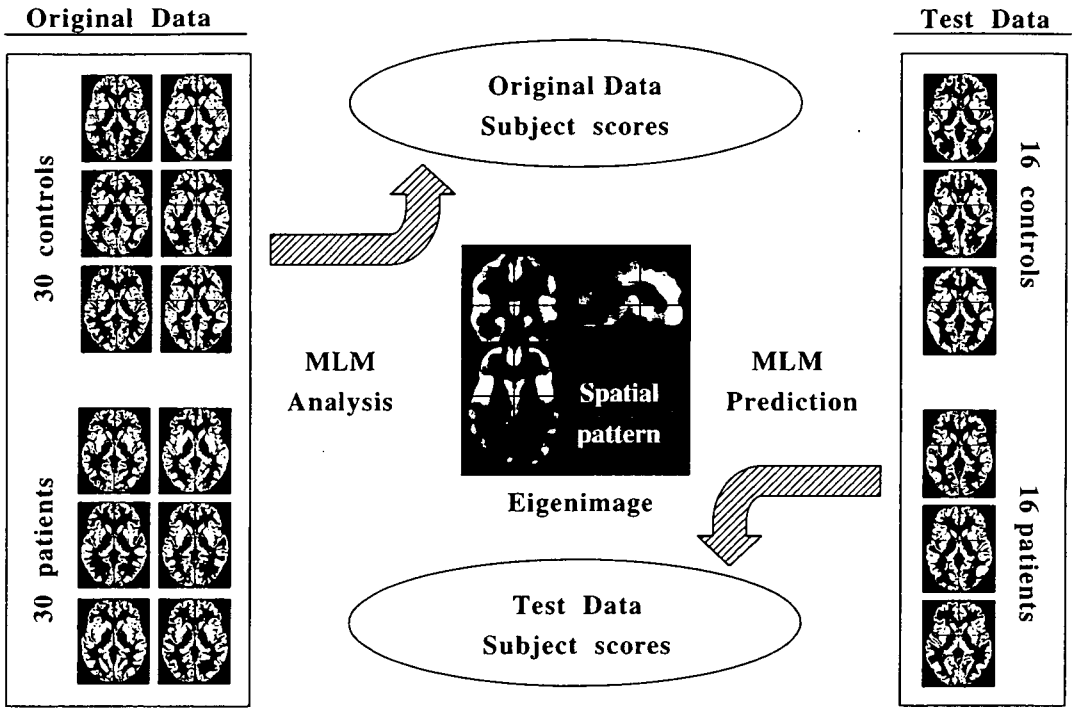

Fig. 1. General scheme of the discriminant function analysis using the VBM and MLM method. An eigenimage and the subject scores were obtained by MLM analysis within the original data. When this eigenimage was used as a predictor of separate data for replication, grouping could be made based on subject scores.

expression of the pattern was applied to classify the MRI scans from the second group with adjustment of individual global values.

Results

Group comparisons in the original cohort using SPM and VBM

Group comparison of gray matter concentrations between the schizophrenia patients and controls is shown in Table 2 and Fig. 2. The results demonstrated that, compared with the control group, the patient group had significantly lower gray matter concentrations in the bilateral medial frontal regions, bilateral lateral frontal regions, bilateral insular regions, and left temporal region. There were no significant regional increases in gray matter concentrations in the patients.

Table 2
Reduced gray matter concentration using SPM99 *T*-statistic

Anatomical region	[area*]	Schizophrenia vs. control				
		T	p-value (corrected)	Coordinates		
				x	*y*	*z*
Medial frontal cortex	[32] Lt.	5.26	0.034	−3	33	21
	[32] Rt.	6.68	<0.001	7	38	25
	[32] Rt.	5.98	0.003	6	50	11
Middle Frontal gyrus	[9] Lt.	5.61	0.011	−45	12	28
Inferior frontal gyrus	[47] Lt.	7.34	<0.001	−35	17	−6
	[47] Rt.	5.64	0.010	44	20	−6
Insular cortex	Lt.	5.16	0.046	−46	2	8
	Rt.	6.40	0.001	40	13	0
Middle temporal gyrus	[21] Lt.	5.87	0.005	−53	−10	−15

Abbreviation: *: corresponding to the area of Brodmann; Rt.: right hemisphere; Lt.: left hemisphere.

Discriminant function analysis using the MLM

The eigenimage, which explained almost all of the total variance with a value of $S=2.672$ ($df=1.57$, $p<0.0001$), was obtained from the first cohort. The pattern of the eigenimage was

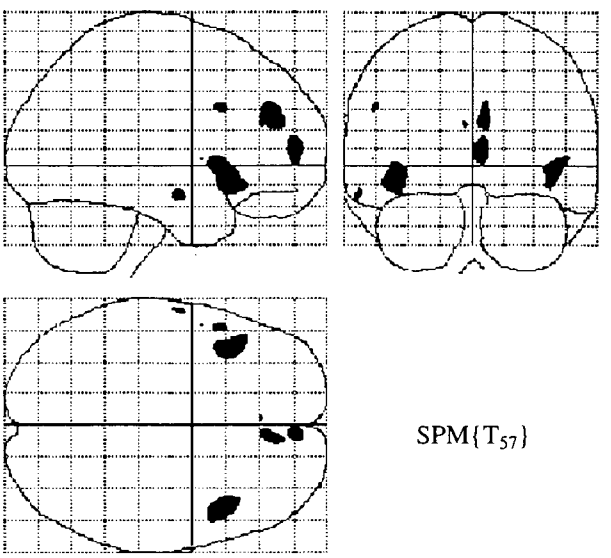

Fig. 2. Distribution of significant voxels with decreased gray matter concentrations in the schizophrenia patients relative to healthy controls. SPM{t} is thresholded at $p<0.05$ corrected for entire volume.

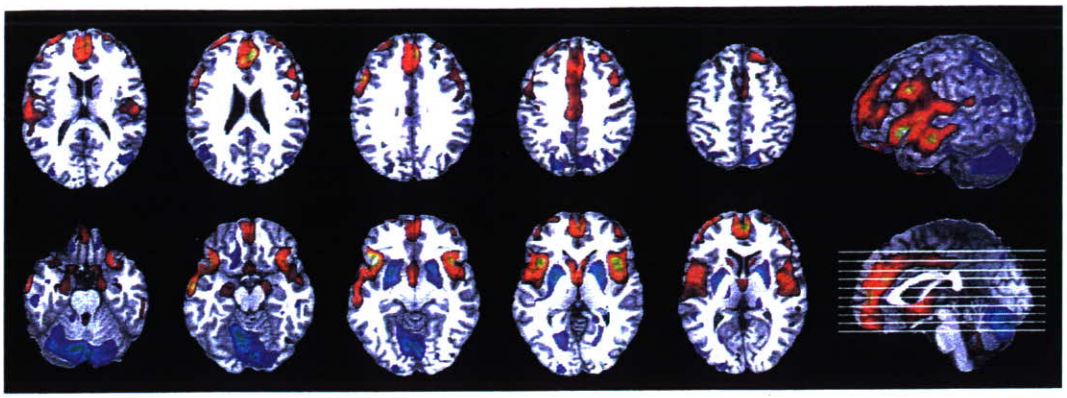

Fig. 3. Eigenimage superimposed on a representative MRI image with the 30% largest loadings for positive (in red) and negative (in blue) loadings.

characterized by positive loadings in the medial and lateral prefrontal regions, insula, lateral and medial temporal regions, and thalamus, and negative loadings in the putamen and cerebellum (Fig. 3). In short, voxels with positive loading in our eigenimage indicated that healthy subjects have more gray matter while patients have less gray matter in those voxels. The contrast of the eigenimage was positive for the healthy controls and negative for the schizophrenia patients. The mean (SD) expressions of the eigenimage were 0.403 (0.308) for the controls and −0.404 (0.369) for the patients. When the demarcation line was set at 0.036 considering the formula to calculate a threshold, 90% of the subjects in the first cohort (i.e., 27 of the 30 control subjects and 27 of the 30 schizophrenia patients, respectively) were correctly classified by this pattern (Fig. 4).

The Jackknife approach was done for each subject of original cohort and more than 75% of the subjects (i.e., 23 of the 30 control subjects and 23 of the 30 schizophrenia patients, respectively) were correctly classified. It was well above 50% of chance accuracy.

Prospective validation

As a prospective validation, the eigenimage derived from the original cohort was used to classify data from a new group of subjects. The mean (SD) expression of the eigenimage with adjustment for the global value was 0.438 (0.330) for the healthy controls and −0.263 (0.226) for the schizophrenia patients. As shown in Fig. 5, more than 80% of the subjects (13 of the 16 control subjects and 14 of the 16 schizophrenia patients, respectively) were correctly classified at the same threshold (i.e., 0.036) of the original discrimination.

Discussion

Several statistical methods have been available for data-driven extraction to define optimal models of predictors, such as the CVA, PLS, and MLM. These methods incorporate a priori information of the model and analyze the covariance structure between the model and the data. They are particularly useful for characterizing the difference between a population of patients and a population of healthy subjects. Because both the sensitivity and the validity of the statistical analysis depend on the choice of the model, they have an advantage over other methods of reducing data dimensionality without a priori knowledge, such as principal component analysis (Bullmore et al., 1996) and Multidimensional Scaling (Welchew et al., 2002). Our data-driven analysis using the VBM and MLM method effectively specified a parsimonious model to distinguish schizophrenia patients from healthy subjects. The correct classification rates in our study were higher than in previous studies, which used volumetric MRI measures (Leonard et al., 1999; Nakamura et al., 2004). The multivariate statistical method (Friston et al., 1996) appears particularly useful for overcoming the limitations of the previous studies due to the limited number of regions of interest. Moreover, the favorable prospective classification of the patients and controls in the new

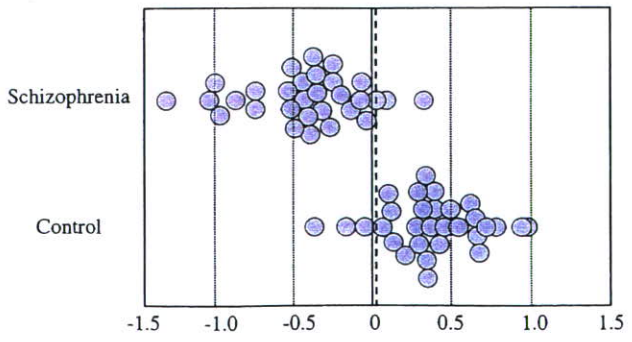

Fig. 4. Expression values of an eigenimage for contrasts between 30 healthy comparison subjects and 30 schizophrenia patients. Dotted line represents demarcation line at 0.036.

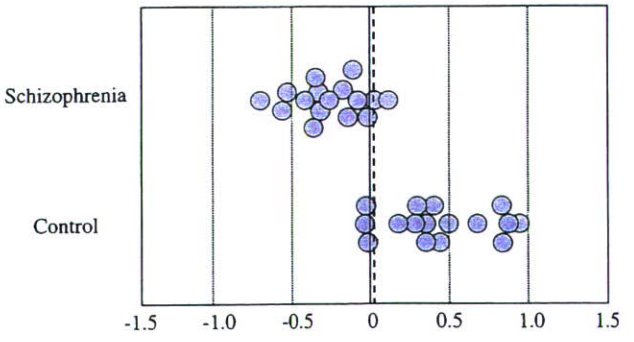

Fig. 5. Post hoc classification of gray matter images of the second cohort with 16 healthy subjects and 16 patients with schizophrenia, based on the eigenimage for contrast between the original comparison subjects and patients. Dotted line represents demarcation line at 0.036.

cohort suggested the practical value of this method as an adjunct to clinical diagnosis.

The analysis in this study uncovered highly significant patterns in putative brain morphological differences between male schizophrenia patients and healthy subjects. The pattern of the eigenimage reflected less gray matter in the prefrontal cortex, medial and lateral temporal regions, insula, and thalamus in the schizophrenia patients compared to the control subjects, and more gray matter in the cerebellar cortex and putamen. A large number of previous VBM studies have identified gray matter deficits in several brain areas in schizophrenia patients, including the lateral and medial frontal regions (Ananth et al., 2002; Gaser et al., 1999; Kawasaki et al., 2004; Kubicki et al., 2002; Moorhead et al., 2004; Sigmundsson et al., 2001; Suzuki et al., 2002) and the superior temporal gyrus and medial temporal structures (Gaser et al., 1999; Kawasaki et al., 2004; Kubicki et al., 2002; Moorhead et al., 2004; Sigmundsson et al., 2001; Suzuki et al., 2002). The schizophrenia patients also had less gray matter in the insula (Kawasaki et al., 2004, Kubicki et al., 2002, Sigmundsson et al., 2001; Wright et al., 1995) and thalamus (Ananth et al., 2002, Gaser et al., 1999). The results of the group comparisons in our study also replicated the previous finding that schizophrenia patients have reduced gray matter concentrations in the medial and lateral frontal regions and insula. Although the group comparison failed to disclose a significant difference in some regions such as the bilateral medial temporal gray matters and thalamus, the pattern of the eigenimage sufficiently reflected these regional gray matter reductions. The discrepancy may be due to a difference in statistical procedure between the standard group analysis by AnCova of VBM and similarity measures of MLM (Kherif et al., 2003); the former allows us to detect focal changes while the latter is more sensitive to extensive regions of connected voxels (Worsley et al., 2005). Thus, present MLM method utilized all of the pertinent regional characteristics.

Another possible implication of the present results is that abnormalities in the connectivity of brain structures comprising regionally distributed neural systems may provide a basis for interpreting the spatial characteristics of pathological changes in schizophrenia. In other words, the specific pattern of the eigenimage may reflect abnormal structural connectivity between regions where correlative changes in gray matter concentration take place. In fact, there has been evidence of altered integrity or volume reduction of the white matter tracts in schizophrenia, such as those in the uncinate fasciculus, cingulum bundle, and anterior limb of the internal capsule (Kubicki et al., in press; Suzuki et al., 2002; Zhou et al., 2003), and these findings have been related to fronto-temporal or fronto-thalamic disconnectivity. Anatomical disconnectivity between the frontal and temporal cortex has also been observed in inter-regional correlational studies in schizophrenia (Bullmore et al., 1998; Mitelman et al., 2005). The eigenimage in this study may represent a perspective of the morphological substrates for abnormal functional connectivity between several brain regions that have been reported to play critical roles in the pathophysiology of schizophrenia (Andreasen et al., 1996; Fletcher et al., 1999; Friston and Frith, 1995; Kurachi, 2003; Lewis and Lieberman, 2000; Meyer-Lindenberg et al., 2001).

A few limitations of the present study must be taken into account. First, this study included only male subjects. In view of the gender differences in brain morphology reported in normal subjects as well as in schizophrenia patients (Collinson et al., 2003; Good et al., 2001b; Suzuki et al., 2002), the correlative changes in gray matter distribution in female subjects need to be investigated separately. Second, it is difficult to address the specificity of the present findings. Further studies that include patients with other schizophrenia spectrum disorders or mood disorders should be conducted to assess their specificity. Third, effects of healthy aging (Good et al., 2001a; Narr et al., 2003) and intelligence (Paradiso et al., 1997), factors associated with the stages of the illness (DeLisi, 1999; Lieberman et al., 2005; Pantelis et al., 2003), and typical or atypical antipsychotic medications (Dazzan et al., 2005; Lieberman et al., 2005) may have affected the gray matter distribution, and interactions with these factors may have compromised its ability to recognize the regional differences. Possible sub-threshold histories of substance taking must be considered, although none of the present patients were diagnosed as having substance abuse disorders. Further refinement, for example, by including these factors in the statistical model may improve the classification. Fourth, image processing using SPM99 is rather old and segmentation algorithms have been improved in SPM2 and updated in SPM5. Moreover, an optimized VBM method has been proposed to avoid errors of interpretation caused by misclassification of non-brain voxels (Good et al., 2001a). These improvements would bring about VBM as a tool for detecting subtle structural brain changes more accurately.

Application of the multivariate statistical methods to the VBM data revealed a significant correlative pattern of brain gray matter distribution that discriminated between the male patients with schizophrenia and the male control subjects. This pattern allowed favorable classification of subjects into different groups. Further elaboration of the present method may contribute to the clinical diagnosis of schizophrenia in the future.

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Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: A preliminary report

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Abstract

A longer duration of untreated psychosis (DUP) in schizophrenia is reported to lead to a poorer clinical outcome, possibly reflecting a neurodegenerative process after the onset of overt psychosis. However, the effect of DUP on brain morphology in schizophrenia is still poorly understood. In this study, we used magnetic resonance imaging to investigate the relation between DUP and volumetric measurements for the superior temporal sub-regions (Heschl's gyrus, planum temporale, and caudal superior temporal gyrus), the medial temporal lobe structures (hippocampus and amygdala), and the frontal lobe regions (prefrontal area and anterior cingulate gyrus) in a sample of 38 schizophrenia patients (20 males and 18 females) whose illness duration was less than five years. We found a significant negative correlation between DUP and the volume of gray matter in the left planum temporale even after controlling for age, age at illness onset, and duration and dosage of neuroleptic medication. There was no such correlation for the other brain regions including each sub-region of the prefrontal cortex (the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, ventral medial prefrontal cortex, orbitofrontal cortex, and straight gyrus). When subjects were divided into two groups around the median DUP, the long-DUP group had a significantly smaller planum temporale gray matter than the short-DUP group. These findings may reflect a progressive pathological process in the gray matter of the left planum temporale during the initial untreated phase of schizophrenia, whereas abnormalities in the medial temporal regions might be, as has been suggested from previous longitudinal findings, relatively static at least during the early course of the illness.
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1. Introduction

Brain morphologic abnormalities in schizophrenia have already developed by the onset of psychosis (reviewed by Shenton et al., 2001; Vita et al., 2006),

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suggesting a neurodevelopmental pathology (Weinberger, 1987). On the other hand, recent follow-up magnetic resonance imaging (MRI) studies have demonstrated progressive changes in the initial years subsequent to the onset of schizophrenia in the left superior temporal gyrus (STG) (Kasai et al., 2003a,b) and the frontal lobe (Gur et al., 1998; Ho et al., 2003b) but not in the medial temporal lobe structures (Wood et al., 2001; Kasai et al., 2003a). Interestingly, Ho et al. (2003b) suggested progressive ventricular enlargement in the early course of schizophrenia to be associated with a poorer clinical outcome. These longitudinal observations support that a subset of brain abnormalities may be associated with neurodegenerative processes after the onset of psychosis at least in a subgroup of schizophrenia, but the factors that influence these processes remain unclear.

A longer duration of untreated psychosis (DUP), which is defined as the time from manifestation of the first psychotic symptoms to the initiation of neuroleptic treatment, has been reported to be associated with treatment resistance and poor clinical outcome (reviewed by Marshall et al., 2005; Perkins et al., 2005), possibly reflecting the adverse neurotoxic effect of psychosis prior to the treatment (Keshavan, 1999). However, the effect of DUP on brain morphologic abnormalities in schizophrenia is still poorly understood. In an earlier volumetric MRI study of untreated first episode schizophrenia patients, an inverse correlation between pre-treatment illness duration and the volume of the left STG was reported (Keshavan et al., 1998), but subsequent studies failed to find a significant correlation between the DUP and morphology in whole brain (Fannon et al., 2000; Hoff et al., 2000; Hietala et al., 2003; Ho et al., 2003a), the frontal (Hietala et al., 2003) and temporal (Fannon et al., 2000; Hoff et al., 2000; Hietala et al., 2003) lobes, or the hippocampus (Ho et al., 2005). Using voxel-based morphometric analyses of MRI, Lappin et al. (2006) demonstrated that gray matter reductions for the left temporal and occipital regions are more marked in psychotic patients with a long DUP. However, their sample characteristics as well as definition of DUP were different from those of other studies; they defined the first contact with mental health services as treatment onset and included a more diverse population with a less severe psychosis. Thus, further studies are warranted to clarify the association between DUP and brain morphology in schizophrenia especially for the specific regions of the brain such as the left posterior portions of the STG, where progressive morphologic changes after the onset of psychosis have been demonstrated (Kasai et al., 2003a,b). To our knowledge, however, no brain morphologic studies have examined volumetric changes in the specific subregions of the STG in relation to the length of DUP in schizophrenia.

In the present study, we used MRI to investigate the relation between the DUP and brain morphologic abnormalities in schizophrenia patients whose duration of illness was less than five years. Regions of interest (ROIs) for the volumetric measurements were placed in the superior temporal sub-regions and the medial temporal and frontal lobe structures because we have previously found significant volume changes in these regions (Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006). We predicted from previous cross-sectional (Keshavan et al., 1998; Hietala et al., 2003; Ho et al., 2005) and longitudinal (Wood et al., 2001; Kasai et al., 2003a,b) observations that the DUP of schizophrenia patients would be related to volume in the left STG but not in the medial temporal and frontal lobe regions.

2. Methods

2.1. Subjects

Right-handed schizophrenia patients who met the ICD-10 criteria for research (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital. Diagnoses were made following structured clinical interviews by psychiatrists with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Clinical symptoms were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b). The patients who underwent an MRI scan were screened for study eligibility by an experienced psychiatrist (TT) on the basis of a structured clinical interview and exhaustive review of the clinical records. Whenever possible, a close family member of the patient was interviewed by psychiatrists to provide additional information. Inclusion criteria were: (1) a duration of illness of less than five years; (2) time point of the illness onset defined by the beginning of delusions, hallucinations, or marked formal thought disorder could be identified; and (3) not receiving neuroleptic medication prior to the onset of overt psychosis. The study population was not restricted to first-episode schizophrenia patients because we intended to include a sufficient sample of patients to cover a broad range of DUP values. The DUP was

defined as the duration in months from the illness onset to the initiation of antipsychotic treatment (Hoff et al., 2000). The time point of the onset of psychosis was identified using all available clinical data obtained from a detailed review of the clinical records and from interviews with the patients and their close relatives. The inter-rater intraclass correlation coefficient (ICC) for the assessment of DUP in our laboratory was 0.91.

Of the initial 62 patients for whom volumetric data were available, four patients were excluded because they had been on neuroleptic medication before the apparent onset of schizophrenia for their prodromal symptoms, and five were excluded because of limited information relating to their illness onset. Among the remaining 53 patients [26 males and 27 females, mean age=25.6± 4.8 years, mean illness duration=43.9±46.6 months (range=1.0–168.0), mean DUP=9.4±18.8 months (median=2.0, range=0.1–120)], 38 patients with a duration of illness of less than five years (20 males and 18 females) remained eligible; their mean illness duration and mean DUP were 18.8 months (S.D.=15.7, range=1.0–48.0) and 6.6 months (S.D.=10.7, median=2.0, range=0.1–47.0), respectively. Fourteen of the 38 patients were outpatients, and 24 patients underwent an MRI scan during admission. Ten of the 38 patients came to the university hospital directly, and the other 28 were referred; 21 patients from psychiatrists and seven by way of others (e.g. other services in the same university hospital). All patients have consistently received adequate clinical follow-up for more than six months after the onset of illness, and none of the 38 patients' diagnosis has changed during the follow-up period (mean follow-up period after MRI scanning=3.5 years, S.D.=2.1). Of the 38 patients, 27 were diagnosed with paranoid schizophrenia, 10 with undifferentiated schizophrenia, and 1 with catatonic schizophrenia. They were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, or substance abuse. All but one of the female patients were on neuroleptic medication at the time of scanning; 15 were being treated with typical neuroleptics (8 males, 7 females) and 22 (12 males, 10 females) were receiving atypical ones. There was no significant difference in the gender ratio between the typical and atypical groups (chi-square test, chi-square=0.01, P=0.942). Demographic and clinical data of the subjects are shown in Table 1. Although the male patients were significantly taller (male patients, 170.2± 4.5 cm; female patients, 157.4±3.8 cm; ANOVA, F=81.09, df=1, 36, P<0.001) and heavier (male patients, 64.3±13.7 kg; female patients, 50.9±6.3 kg; ANOVA, F=14.54, df=1, 36, P<0.001) than the female patients, there were no significant differences between male and female patients in age, education, parental education, age at onset, DUP, duration of illness, duration of medication, and medication dosage. There were no significant differences between male and female patients in the total score or the subscale scores for SAPS and SANS.

This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

MRI scans were acquired with a 1.5-T Magnetom Vision (Siemens Medical System, Inc, Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256×256 pixels. The voxel size was 1.0×1.0×1.0 mm^3.

Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc, Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (Asahi Kasei Joho System Co, Ltd, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition

Table 1
Clinical and demographic characteristics of patients with schizophrenia

	Schizophrenia patients (N=38)
Male/female	20/18
Age (years)	24.1±4.3 (range, 18.3–32.7)
Height (cm)	164.1±7.7
Weight (kg)	57.9±12.7
Education (years)	13.5±1.8
Parental education (years)	12.5±2.2
Age at onset (years)	22.6±4.6
Duration of untreated psychosis (months)	6.6±10.7 (median=2.0)
Duration of illness (months)	18.8±15.7
Duration of medication (months)	11.8±15.7
Drug dose (mg/day, haloperidol equiv.)[a]	10.8±7.8
Total SAPS score	23.5±19.4
Total SANS score	49.9±25.0

The values represent means±S.D.s.
SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] The different typical and atypical neuroleptic dosages were converted into haloperidol equivalents using guidelines established by Toru (2001).

and were then reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003).

2.3. Volumetric analyses of regions of interest (ROIs)

Fig. 1 shows the ROIs observed in this study. The gray matter volumes of the superior temporal subregions [Heschl's gyrus, planum temporale, and caudal superior temporal gyrus (STG)] and the frontal lobe structures (prefrontal cortex and anterior cingulate gyrus) were obtained by using the above-mentioned segmentation procedure. For the medial temporal lobe structures (amygdala and hippocampus), volumes of gray and white matter were measured together. We selected these ROIs because of significant volume reductions in schizophrenia as demonstrated in our previous publications (Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006). Each ROI was manually traced on 1-mm consecutive coronal slices with the corresponding sagittal and axial planes simultaneously presented for reference.

2.3.1. Superior temporal sub-regions

As described previously (Takahashi et al., 2006), we first traced the whole STG and segmented it into supratemporal and lateral portions by the lateral limb of the supratemporal plane. The whole STG was traced posteriorly to the end of the horizontal limb of the sylvian fissure. Heschl's gyrus was traced posterior to

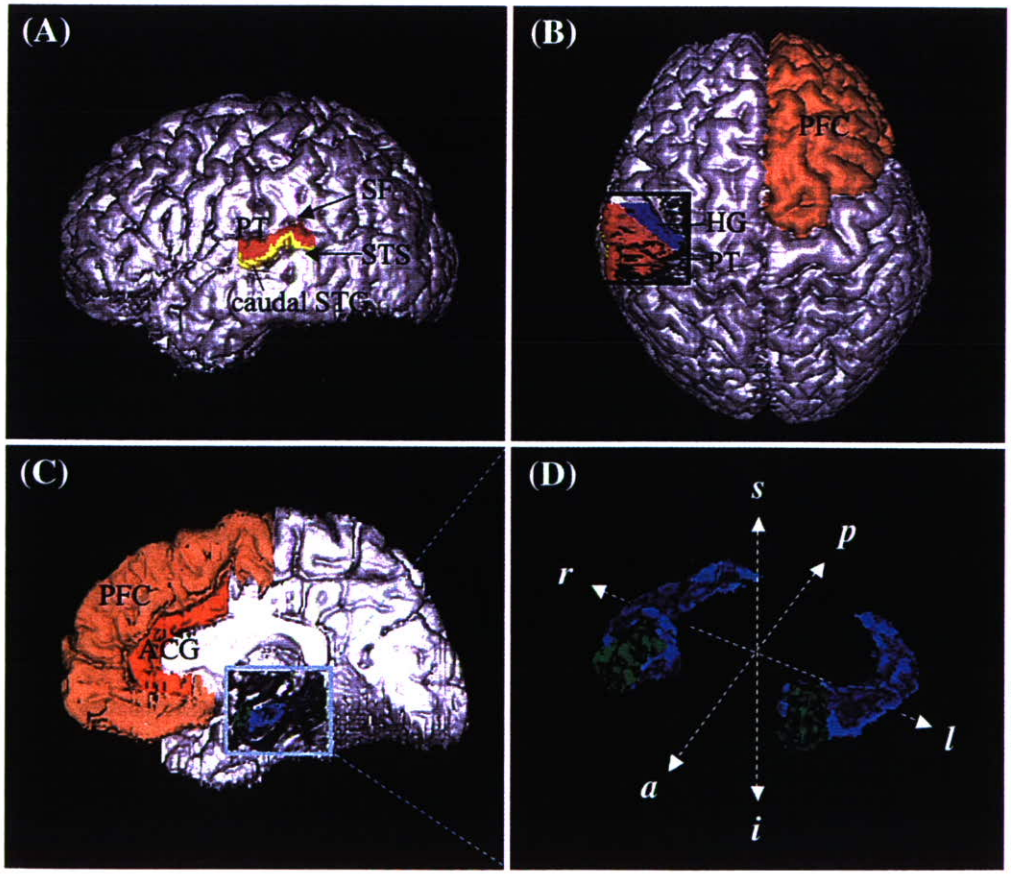

Fig. 1. Three-dimensional reconstructed images of regions of interest (ROIs) presenting lateral (A), dorsal (B), and medial (C) views of the brain. The parietal lobe in panel B and the temporal lobe in panel C are partially cut off to disclose the ROIs examined. Panel D shows a reconstructed image of the amygdala (green) and hippocampus (light blue). Detailed delineation methods for each ROI (Niu et al., 2004; Suzuki et al., 2005b; Zhou et al., 2005; Takahashi et al., 2006) and for the sub-regions of the prefrontal cortex (Suzuki et al., 2005b) have been described in our previous publications. Abbreviations: a = anterior; ACG = anterior cingulate gyrus; HG = Heschl's gyrus; i = inferior; l = left; p = posterior; PFC = prefrontal cortex; PT = planum temporale; r = right; s = superior; SF = sylvian fissure; STG = superior temporal gyrus; STS = superior temporal sulcus.