特集 情動の脳科学

統合失調症：自己意識の障害と社会性関連回路*

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磁気共鳴画像の計測からは，統合失調症の患者群では健常者群に比較して，とくに辺縁系（扁桃体，海馬），傍辺縁系皮質（島回，帯状回），上側頭回，背外側前頭葉などに灰白質体積の減少が示されている。言語野とmirror neuronシステムを構成するSylvius周辺構造もその中に含まれ，左優位半球の方に変化が強い。統合失調症の臨床症状では，自己意識の障害が特徴的である。この自己意識の障害はmirror neuronシステムと関係があるかも知れない。今後，その病態解明を進めるとともに，脳の形態学的変化を治療し得る薬剤の開発が，統合失調症研究の重要な課題である。

キーワード：統合失調症（schizophrenia），自己の障害（disturbance of the self），mirror neuron，Sylvius周辺構造（peri-Sylvian structures）

はじめに

統合失調症の発病危険率は一般人口の120人に1人で，20歳から25歳にかけて発症年齢のピークがある。統合失調症では常識的な理解を超える症状が現れるが，その代表的なものは，「自己」に関する障害（disturbance of the self）である。健常者にとっては，自分が考え，自分の言動は自分の意志に基づき，自分という人間はこの世に1人で，他人とは一応別の存在である，ということはほとんど自明のことがらである。しかし，この自己の成立が統合失調症では障害される。

この自己意識（self-awareness）は，長い間哲学や精神病理学の考察の対象にとどまっていた。しかし，近年では認知神経科学の課題としても取り上げられるようになり（Decety & Sommerville, 2003），統合失調症の自己意識の障害についても脳画像を用いて，解明の手がかりが得られつつある。正常機構はしばしば病的機構を通じて解明されることから，統合失調症研究は，健常者の自己と社会性の脳内機構の解明にも大きく貢献すると思われる。

ここでは，このような視点から，統合失調症の自己意識の障害，脳の形態学的変化，臨床症状との関連，2段階発症仮説，および健常者の社会的認知と自己認知について述べることにしたい。

Ⅰ．統合失調症の自己意識の障害

統合失調症では様々な症状が生じるが，Schneider（1976）は統合失調症の診断に重要な症状を一級症状として取り出し，これは今日の診断基準でも重視されている。Schneiderの一級症状は表1のごとくで，それぞれが他の症状からは導き出されない症状として精選されている。これらは何らかの点で「自己」に関する障害であり，Schneider自身も「自我性（Ichhaftigkeit），あるいは自己所属性（Meinhaftigkeit, sense of mine）の障害，すなわち，自己の心的作用や状態が，自分のものとして体験されずに，他人から支配され影響される

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* Schizophrenia：disturbance of the self and sociality-related circuits.

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表1　Kurt Schneider (1976) の一級症状

一級症状	Schneider の記述 (Wing et al, 1974 の説明)
考想化声	「自分の考えが聞こえてくること」
会話形式の幻聴	(自分のことを3人称でうわさをしている1人または複数の声が聞こえる)
自分の行為を批評する声の幻聴	例えば,「そら，またガツガツ食べるよ」
身体的被影響体験	「よく器械や光線や電気などの影響であるかのように考えられる。性的な性質を帯びることが多い。」
思考奪取，そのほか思考への干渉	「考えが抜き取られる。」思考干渉の例として,「自分の考えたくないことや悪いことを考えずにはいられない。」
考想伝播 (Gedankenausbreitung)	「考えが自分1人のものではなく，他人がそれに関与している(同じ部屋にいない人にまで自分の考えが伝わってしまう)。」
妄想知覚	「実際の知覚に，合理的または情緒的な了解可能な原因なしに，異常な意味一多くは自分と関係があるような一が与えられた場合をいう。」
感情，意欲や意志の領域における他からの作為 (させられ) や被影響のすべて	「行為，感情，あるいは欲動が，他からさせられ，影響され，支配される。」

ものとして体験されるという障害」が統合失調症にきわめて特徴的であると述べていた。この自己意識の障害の中で，代表的なものは,「させられ体験」と「考想伝播」である。

「させられ体験」とは,「本人の意志が，外部の何ものかによって取って代わられている」という体験で,患者は,「自分自身ではない他の力によって，自分が支配されている」,「まるで意志を持たないロボットか抜け殻みたいに」感じる。

考想伝播とは,「考えることが自分一人のものではなく」,「自己の考えが,同じ部屋にいない人にまで伝わっているという体験」であり，患者は，時には，自分の考えが日本中や世界中に伝わっていると述べる。Jaspers (1959) が述べているように「その体験の基礎には，自己と周囲の世界との境界が失われたことにあるにちがいない」。これは他の症状，例えば考想化声 (自分の考えが誰かの声となって聞こえてくること) から二次的に導かれるのではなく，患者の直接的な体験であることが重要な点である。そうでなければ，自己の境界の障害という考え方は出てこない。実際に，考想化声のない患者が考想伝播を示すことも稀ではない。筆者が，自分の考えが世界中に伝わっているという患者に,「では，言葉の問題はどうなるの？」と聞くと，患者によれば,「そういう問題ではないんだ」ということであった。

このように自己の精神活動の自己所属性が失われるだけでなく，他者性を帯びるのが統合失調症の体験の大きな特徴である。統合失調症の前駆期に,自生観念，すなわち自分のものではない考えが頭に浮かんでくるという症状が生じることがある。この段階では，自己所属性は失われていても，他者性を帯びるところまでは進行していない。

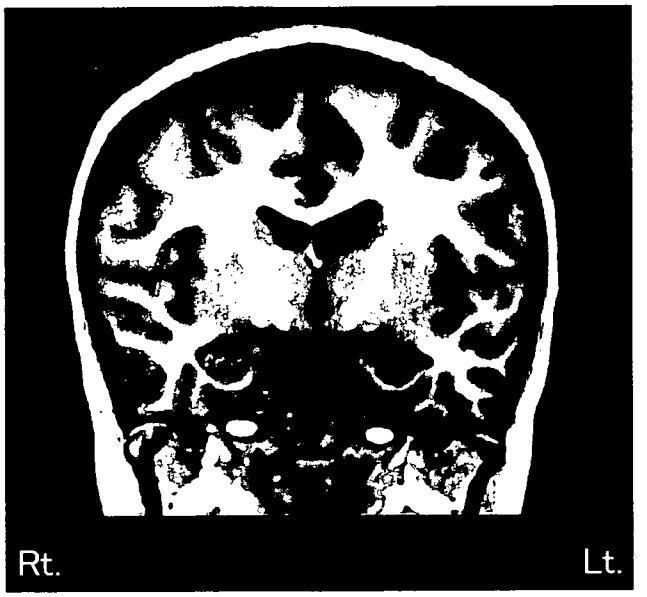

図1　統合失調症患者 (19歳，女性) の MRI
左の側脳室と下角，および第3脳室に軽度の拡大がみられる。

II. 統合失調症の脳の形態学的変化

このように独特の症状を呈する統合失調症では，脳に形態学的・機能的な変化が生じているのではないかということは,長い間仮説にとどまっていた。しかし，Johnstone ら (1976) が CT を用いて，統合失調症患者の脳室拡大を報告して以来，非常に多くの形態画像研究がなされ，統合失調症患者群では，健常対照群と比べて，脳に軽度の形態学的変化のあることが明らかになった。1988年から2000年までの193編の，統合失調症の磁気共鳴画像 (MRI) 研究 (関心領域法) を集計

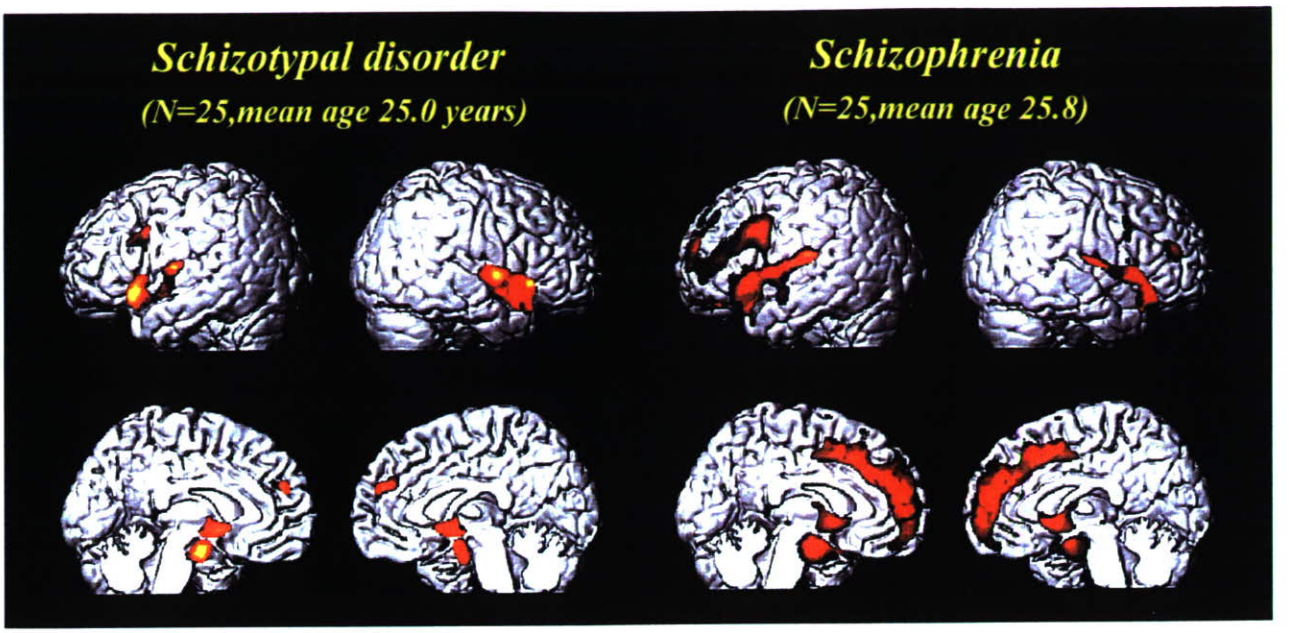

図 2　統合失調型障害患者（左）と統合失調症患者（右）における脳灰白質密度の減少部位（Kawasaki ら，2004）
健常者群と比較し，各群において灰白質の減少が認められたボクセルを標準脳上に赤色で示す（height $p<0.0001$, uncorrected）。

した Shenton ら（2001）の総説では，統合失調症患者群では，健常対照群と比べて，側脳室の拡大（80%：有意差を認めた報告の%），第3脳室拡大（73%）の他，内側側頭葉構造（扁桃体，海馬，海馬傍回）（74%），上側頭回（100%），前頭葉（59%）などで体積の有意な減少が報告されていた。図1は，19歳女子の患者の脳MRIである。この画像は，統合失調症的脳の特徴をよく示しているように思われる。すなわち，左の側脳室が明らかに拡大し，下角も拡大している。第3脳室も丸みを帯びて，軽度に拡大している。

MRIを用いて脳の形態学的変化を検討する方法としては，関心領域法と画像統計解析法がある。関心領域法も，近年は高分解能三次元（3-D）MRIを用いて脳回ごとの計測が行われ，精度が向上してきている。画像統計解析法の代表的なものは，statistical parametric mapping（SPM）である。これには解剖学的標準化という処理が入るが，体積の差はvoxelごとの密度（density）の差に変換され，voxel-based morphometryとも呼ばれる。

Suzuki ら（2002）は，統合失調症患者45例と健常者42例を対象に，3-D MRIとSPM-96法を用いて解析した。その結果，健常対照群に比べて，統合失調症患者群では，左半球の上側頭回と中・下前頭回，右半球の下前頭回領域に灰白質密度の減少があり，内側面では，両側半球の海馬と前部帯状回を含む内側前頭葉領域の灰白質密度の減少が認められた。これらの領域は，Shenton ら（2001）がまとめている関心領域法を用いた報告とほぼ一致していたが，内側前頭皮質の変化がより明瞭に示された。その後，SPM-99を用いて統合失調型障害と統合失調症を比較した結果では，側頭葉の変化は両群に比較的共通していたが，統合失調症では前頭葉の変化が加わっているのが特徴的であった（図2；Kawasaki et al, 2004）。脳体積の測定としては，関心領域法が絶対値も得られ，より確実である。3-D MRIの1 mm厚の冠状断連続スライスについて，関心領域法で測定した結果の概要を表2に示した。このように辺縁系（海馬，扁桃体），傍辺縁系連合皮質（帯状回，島回），上側頭回，上・中・下前頭回の体積減少があり，左優位半球の変化が強かった。Wernicke野を含む上側頭回の変化は，これまで報告されているとおりである（Hirayasu et al, 1998）。CTで観察されるSylvius裂の開大に対応して，下前頭回，上側頭回と並んで，島回の体積減少も明らかであった（Takahashi et al, 2005）。なお，このような灰白質の体積減少は，患者群と健常者群の平均値の差として認められるものであり，両群は重なりが大きい。

つぎに問題となるのは，このようなmm単位の体積の変化をもたらす神経病理学的変化の性質である。これまで統合失調症の神経病理学的変化については否定的な見解をもつ専門家が多かったが，それは古典的染色法による通常の光顕所見に基づいていたからだと思われる。2005年版のアメリカの標準的な精神医学教科

表 2 統合失調型障害と統合失調症の脳体積の変化：関心領域法による測定結果

領域	統合失調型障害	統合失調症	著者（年）
扁桃体	↓（−15.7/−15.0%）	↓（−12.4/−8.7%）	Suzuki et al (2005b)
海馬	↓（−6.9/−6.5%）	↓（−4.9/−4.6%）	Suzuki et al (2005b)
海馬傍回	→	→	Suzuki et al (2005b)
上側頭回	→	↓（−17.3/−14.7%）	Takahashi et al (投稿中)
島皮質			
前部	→	↓（−8.1/−7.1%）	Takahashi et al (2005)
後部	→	↓（−6.1/−4.9%）	Takahashi et al (2005)
帯状回			
前部	→	↓（→/−13.7%）	Takahashi et al (2004), Zhou et al (2005),
後部		↓（−7.8/−13.1%）	Zhou et al (2005)
上前頭回	→	↓（−7.3/−7.7%）	Suzuki et al (2005)
中前頭回	↑（+7.4/+7.2%）	↓（−5.3%/→）	Suzuki et al (2005)
下前頭回	→	↓（−9.3/−6.5%）	Suzuki et al (2005)
直回	↓（→/−8.8%）	↓（−12.7/−11.8%）	Suzuki et al (2005)

→変化なし；↓減少；↑増加。いずれも健常者群との比較。括弧の数字は健常者の平均値からの差（左/右）

書では，統合失調症の神経病理学として（Roberts & Tamminga, 2005），免疫組織化学的染色などにより，前頭前野皮質などの微細構造の変化，すなわち，前シナプスのマーカーである synaptophysin の30〜50%の減少，GABA 性神経終末のマーカーである GAT（GABA transporter）免疫反応の錐体ニューロン軸索 initial segment での約40%の減少，後シナプスの microtubule-associated protein（MAP2）の31〜42%の減少，神経発達に関するタンパクである reelin の50%の減少，Golgi 染色による樹状突起 spine 数の減少，および palvalbumin で染色される介在ニューロンの減少など，かなり明瞭な所見が述べられている。第2世代抗精神病薬の一部には，形態画像上の変化の進行を防ぐ作用のあることが示唆されているが（Lieberman, 2005），今後は，上述のような微細構造の変化を治療し得る薬剤の探索も必要と思われる。

Ⅲ．臨床症状と脳の形態・機能との関係

臨床症状と脳の形態学的な変化との対応については，いわゆる陰性症状と前頭葉との関連（Chua et al, 1997）だけでなく，幻聴と左の前部上側頭回（Barta et al, 1990），思考障害と左の後部上側頭回（Shenton et al, 1992），陽性症状と海馬・扁桃体の体積減少（Bogerts et al, 1993）が報告されている。その後，Schneider の一級症状と左海馬傍回および右後部帯状回の体積減少との関連も見いだされた（Suzuki et al, 2005a）。抗精神病薬で改善しやすい陽性症状の重症度が，脳の形態学的変化と関連することをどのように考えるかが問題になるが，これらの領域の形態学的変化は陽性症状の発現しやすさや治りにくさ，あるいは脆弱性の程度と関連するのかも知れない。

つぎに Schneider の一級症状と機能画像との関連についての主な報告をまとめたのが，表3である。幻聴とは内言語の過度の活性化であるという仮説がある。実際に，シングルフォトンエミッション CT（SPECT）で局所脳血流を測定すると，活発な幻聴のある患者では，左の上側頭回（言語野）と一次聴覚野（Heschl 横回）が活性化していて，幻聴が消失すると，その活性化も消失することが報告されている（Suzuki et al, 1993；鈴木ら，1999）。このことは，幻聴は患者にとって，真の体験であることを示している。しかし，統合失調症の幻聴には，複数の声が患者のうわさをする会話形式などの特徴があり，言語野だけの活性化で十分に説明できるかどうか疑問が残る。機能的 MRI を用いた Shergill ら（2000）の結果では，幻聴時には，言語野に加えて辺縁系・傍辺縁系が活性化していたという。

させられ体験については，右の下頭頂小葉の過活動との関連が報告されている。させられ体験の認知神経心理学的モデルとして，Frith（1992）は自己モニタリング（self-monitoring）障害仮説を提唱している。させられ体験から出発すれば，Frith のような自己モニタリング仮説が生まれてくるかもしれない。この Frith のモデルについては，Gallagher（2004）の批判がある。

Ⅳ．2段階発症仮説

1．神経発達障害仮説

統合失調症は，当初は青年期に発症する進行性の疾患と考えられていた。しかし，Weinberger（1987），お

表 3 Schneiderの一級症状と主な機能画像所見

症状	方法	MRI所見	報告者(発表年)
幻聴	SPECT	左上側頭回の活性化	Suzuki et al (1993)
	SPECT	Broca野の活性化	McGuire et al (1993)
	fMRI	Heschl回の活性化	Dirks et al (1999)
	MEG	左上側頭回のTheta rhythmの増加	Ishii et al (2000)
	fMRI	両側の上側頭回，左中前頭回，左下頭頂葉の活性化	Lennox et al (2000)
	fMRI	両側の下前頭/島回，前部帯状回，側頭皮質，右視床，左海馬と海馬傍回の活性化	Shergill et al (2000)
	fMRI	幻聴に先行して，左下前頭回と右中前頭回，幻聴中に左下前頭回，両側の上中側頭回と左島回の活性化	Shergill et al (2004)
他者化症候群	SPECT	右頭頂葉と下前頭葉の活性化	Yuasa et al (1995)
させられ体験	PET	右下頭頂葉の活性化	Spence et al (1997)
Schneider一級症状	PET	右上頭頂皮質の活性化，左の後部帯状回と舌状回の低活性	Franck et al (2002)

よびMurrayとLewis (1987)によって神経発達障害仮説が提唱され，広く受け入れられている。神経発達障害仮説の根拠としては，①形態学的変化は初発の統合失調症患者でも認められる，②側脳室の拡大は罹病期間と相関しない，③皮質，あるいは皮質下白質に神経発達(神経細胞の遊走)障害を示唆する細胞構築学的変異がみられ，④それは，グリオーシス(修復機転としてのグリア線維の増殖)を伴っていない，などが挙げられる。

神経発達障害仮説については，人生早期(胎生期・出産期)の障害を想定する初期神経発達障害仮説と，青年期の脳の成熟障害を重視する後期神経発達障害仮説がある。近年では，初期と後期の神経発達障害仮説を合わせた2段階仮説(two-hit model)を受け入れる研究者が多い。

2. 側頭-前頭2段階発症仮説

側頭-前頭2段階発症仮説(倉知ら，2001，2005；Kurachi, 2003a, b)とは，明らかな統合失調症症状を示すには至っていない統合失調型(人格)障害と，統合失調症の脳形態の比較から導かれたもので，「側頭葉の変化は統合失調症への脆弱性に関連し，それに前頭葉の変化が加わると，側頭葉機能障害が臨床的に顕在化し，統合失調症の症状が発現する」という考えである。Siever (2002)，SieverとDavis (2004)も最近，われわれと同様に統合失調症における前頭葉の変化を重視している。他方，初発統合失調症で，上側頭回の進行性の体積減少も報告されているので(Kasai et al, 2003a, b)，上側頭回の変化は脆弱性に関連するとしても，その後も進行する可能性がある。

本仮説をさらに詳しく述べると(図3)，統合失調症患者では，おそらく病前から存在する主として側頭葉の変化によって，認知の枠組み(frame)に偏りが生じ，それが病前の行動特徴となって現れるのであろうと推定される。このような内側側頭葉構造の変化が統合失調症への脆弱性を形成し，動物モデル(Uehara et al, 2000, 2003；Sumiyoshi et al 2004, 2005)からも支持されるように，辺縁系のドーパミン(DA)過剰伝達を生じやすくしているようである。

患者の病前の行動特徴として，本人から「人と合わせることができなかった」とか，家族から「小学生時代に，家族がある話題で盛り上がっているときに，ピントはずれなことを言ってみたりすることがあった」と述べられるのは，認知の枠組みの偏りの例とみなされよう。疎通性の程度とは，お互いにどの程度共通の基準枠(frame of reference)を形成，あるいは駆動できるかということによると思われる。認知の枠組みの偏りがあると，人とうまく合わせることができず，ストレスを感じやすくなると思われる。

思春期後期や成人前期にかけて，このようなストレスの蓄積や内側・背外側前頭葉の変化が加わることにより，扁桃体など辺縁系のDA過剰伝達が生じる。それにより，社会性関連回路(sociality-related circuits)が変調をきたし，幻聴や自己意識の障害などの統合失調症の症状が顕在化するのではないかという考えである。

いわゆる陰性症状については，これまでの画像研究からは，主として前頭葉の機能障害と関連することはほぼ明らかである(鈴木と倉知，1993)。側頭葉の変化がほとんどなくて，前頭葉の変化が青年期以降に生じると，単純型統合失調症(陰性症状が主で，陽性症状をほとんど示さない稀な類型)になるのかも知れない。実際に，Suzukiら(2005c)の研究では，単純型統合失

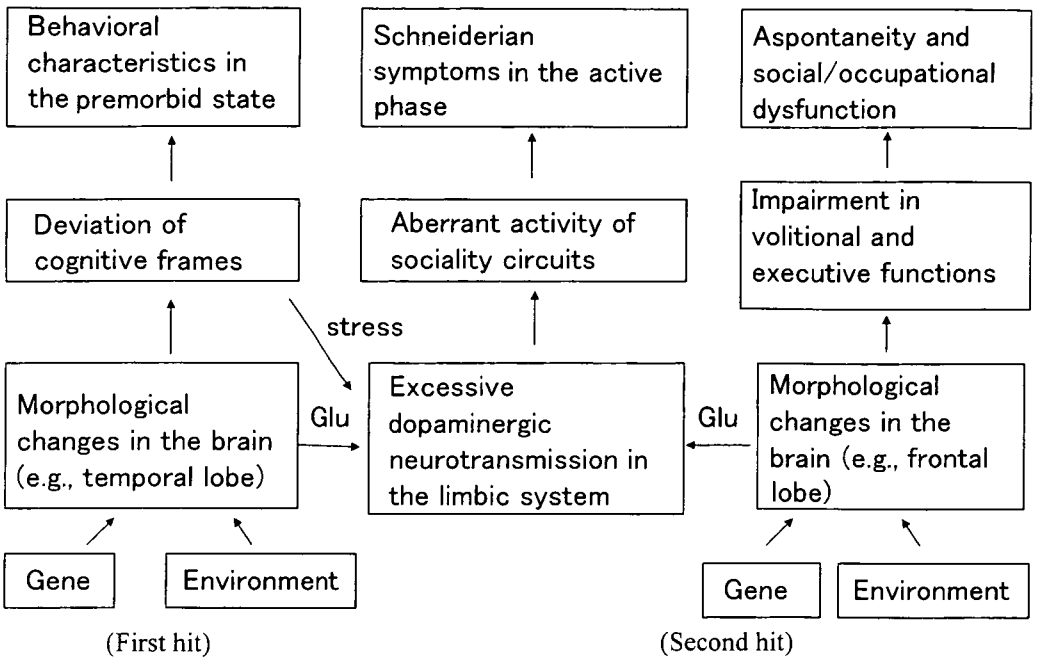

図 3 側頭-前頭2段階発症仮説
Kurachi (2003b) より一部改訂。

調症では，統合失調症に比べて，前頭葉の変化がさらに著明であった。この考え方は，前頭葉の病変は，Crow (1980) の臨床記述的な意味での陰性症状（正常機能の低下：感情平板化，発話の貧困，意欲減退）を発現させるとともに，側頭葉の潜在的な変化を陽性症状（異常な心理的様相：幻覚，妄想，思考障害）として顕在化させるという点では，Jackson (1884) の神経系の階層的観点からの陰性症状（上位の抑制性機能の障害）という役割も果たすことになる（図3の右）。これがほとんどの統合失調症でCrowのいう陰性症状と陽性症状がともに存在する理由かも知れない。

3. 認知の枠組みの障害

認知の枠組み (frame) とは，様々な情報を整理整頓し，秩序づける（自己組織化する）際に必要となるカテゴリー構成のことを指している。脳はそれらをあらかじめ有しているか，それらを形成する仕組みを有していて，それによって，認知が成立すると考えられる。統合失調症では，この認知の枠組みの形成が，健常者を基準にすれば，偏っているようである。

統合失調症患者の認知神経心理学的機能の障害は，記憶，管理実行機能，および注意の障害とまとめることができる。その中でも最も一定しているのは，軽度の記憶障害であることが指摘されている（倉知と住吉，1999；Matsui et al, 2004）。木場ら (1988) が，Wechsler記憶尺度の日本語版を作成し，知能指数 (IQ) 90以上の統合失調症患者に施行した結果でも，この患者群では，注意力を表すとされる数唱問題は保たれているのに対して，とくに論理的記憶（物語の記憶）が有意に低い値を示し，知的水準や検査態度からは説明できない記憶障害があることが示された。

統合失調症患者におけるこのような記憶障害の主な要因は，記憶の組織化（体制化：organization），すなわち，素材をまとめ上げることの困難さにあるようである。記憶の組織化は，単語記憶テスト（山下ら，2000）で測定することができる。そのunblocked listでは，16個の単語がそれぞれ4つのカテゴリーに分かれているが，同じカテゴリーの単語は連続しないように呈示される。これらの単語の再生に際しては，健常者では，同じカテゴリーに属する単語をまとめて再生する傾向があるが，患者ではそれが乏しい。この言語記憶の組織化は，左の下前頭回領域の賦活と関連することが示唆されている（Fletcher et al, 1998；Nohara et al, 2000）。

単語の組織化は，動物名の列挙のような語流暢性課題でも調べることができる。Sumiyoshi Cら (2001) がカテゴリーの意味構造について，動物名の列挙の順序を多次元尺度法で解析した結果，健常者では，2つの次元に分布し，その1つの軸は家畜性対野生と解釈された。しかし，統合失調患者では，このような次元の存在は明らかではなかった。なお，serotonin (5-HT) 1A partial agonistの併用（Sumiyoshi T et al, 2001）や第二世代の抗精神病薬による治療（Sumiyoshi et al, 2005 Epub；Araki et al, in press）により，このような記憶の

組織化が改善されることが報告されている。

このような情報の自己組織化は，脳活動の基本的な特性のようである。「混沌から秩序へ」という作業は，おそらく意識下や睡眠時でも続けられていて，自己意識とは脳の自己組織化によって生成される最終的な到達点なのかも知れない。そして，統合失調症では情報の自己組織化の障害の結果，統一的な自己の生成が障害されるのかも知れない。

4. 自他の縮図の脳内表現（representation）としての社会性関連回路

「自分の考えより先に言葉が浮かんできて，口を動かさなくても，その言葉が周りの人に聞こえているように思う」。これは，ある統合失調症患者（27歳，女性）の言葉である。これを論理的に説明するためには，どのようなモデルが考えられるだろうか。

社会性関連回路（sociality-related circuits）とは，統合失調症のこのような「自己」の障害から導かれた考えである（倉知，1998，2003b）。統合失調症における他者性の出現を，Frithのように自己所属性の喪失に伴う患者の誤った説明という見方もあり得るが，そうではなくて実体的な生き生きとした体験を患者が述べていると受けとることもできる。もし，実体的な体験ととれば，人間の脳内には，自己と潜在的他者の縮図の表現（representation）があり，この潜在的他者の活動が亢進し，意識上に不特定の他者という形で浮上してきたのが，統合失調症の自己意識の障害であると説明される。この自他の縮図の脳内表現を担う神経回路を「社会性関連回路」と呼ぶことにした。この神経回路の骨格は，おそらく，言語と同様に脳に生得的機構（innate mechanisms；Chomsky, 1965）として備わっていて，母子関係をはじめとする社会的コミュニケーションを通じて形成され，そのはたらきによって，実際の人間関係が実現されると考えられる。

V. 健常者の社会的認知と自己認知

社会性関連回路に関係すると思われるのは，近年見出されたミラーニューロンシステムである。他者の行動を観察する時に，自分がその行動をする時と同じニューロンのセットが活性化し，このシミュレーションによりその個体は他者の行動を理解する。ヒトでのミラーニューロンシステムは，下頭頂小葉，下前頭回弁蓋部（Broca野）とその近傍の前運動皮質のネットワークから形成されている（Gallese et al, 2004）。他者の気持ち（感情）の理解についても，シミュレーションがはたらいていることが示されている（Carr et al, 2003）。Rubyと Decety（2004）の優れた研究によれば，社会的感情（当惑，誇り，恥，罪，イライラなど）が喚起される文章を読む課題では，扁桃体が強く賦活され，それは1人称の視点でも3人称（母親）の視点でも同程度であった。また，他者が痛みを感じる写真を見た時は，両側の前部帯状回と前部島回が強く賦活され，これらは自己の痛みの感覚処理に関する部位でもあるという（Jackson et al, 2005）。

古典的言語野（Broca野，Wernicke野，下頭頂小葉）を構成するSylvius周辺構造が，非言語的な社会的認知を司るミラーニューロンシステムでもあったということは，近年の神経科学の大きな発見であった。このミラーニューロンシステムは，Jacksonと Decety（2004）が述べているように，自他の共表現（shared representation between self and others）ということができる。もし，その領域が何らかの原因で活性化された場合には，その人はどのように感じるだろうか。統合失調症では，反響言語，反響動作，さらには，患者は他者を自己と同一視したりすることがあるが，これらの症状は，ミラーニューロンシステムの機能状態との関係で解明されるかも知れない。

自他の区別の問題について，Rubyと Decety（2001, 2003, 2004）は，被験者が3人称視点をとる時には，1人称視点をとる時に比べて，課題の種類（運動，思考，情動）に関係なく，右下頭頂葉と前頭極が賦活されることを示した。また，Farrerと Frith（2002），Farrerら（2003）によれば，視標の動きが自己の制御下にあるという感じが減弱するにしたがって，右の下頭頂小葉が賦活され，島回の活性が減退したという。これらのことから，Deceyと Sommerville（2003）は，自他が共に表現されるネットワークがあり，そこにおける自他の区別には，右の前頭-頭頂のネットワークの関与が重要であると述べている。自己のはたらきは，内側前頭葉の形態と関連する可能性があり（Matsui et al, 2002），自己関連刺激（self-referential stimuli）と大脳の正中構造との関係も重視されている（Northoff et al, 2004）。

おわりに

統合失調症では，常識的な理解が困難な症状が生じるが，そこに人間存在の秘密があるともいえる。統合失調症の患者群では健常者群に比較して，とくに辺縁系（扁桃体，海馬），傍辺縁系皮質（島回，帯状回），上側頭回，上・中・下前頭回などに灰白質体積の減少が認められる。言語野とミラーニューロンシステムを構成するSylvius周辺構造もその中に含まれ，左優位半球の方に変化が強い。統合失調症の臨床症状は様々であるが，とくに自己意識の障害が特徴的である。こ

の自己意識の障害からは社会性関連回路の存在が推定され，それは近年見いだされたミラーニューロンシステムと関係が深いと思われる。今後，その病態解明を進めるとともに，脳の形態学的変化を治療し得る薬剤の開発が，統合失調症研究の重要な課題である。

なお，Jaspers (1959) は，精神病理学総論で，「自我が自己を意識する様式 (der Weise wie das Ich sich seiner selbst bewusst ist)」を自我意識と定義した。その後のドイツや日本の精神医学の教科書 (Huber, 1999；大熊，2005) でも，自我意識 (Ichbewusstsein) や自我障害 (Ichstorung) という用語が用いられている。他方，Jaspers の著書の英訳では，自我意識は自己意識 (self-awareness) と訳され，ドイツから英国に渡った Mayer-Gross の教科書 (1969) でも，自己の障害 (disturbance of the self) と表現されている。本稿では，自己の成立を生物学的に解明していく立場から，自己の方を用いた。

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Abstract

Schizophrenia : disturbance of the self and sociality-related circuits

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Magnetic resonance imaging studies on schizophrenia patients have revealed significant grey matter volume reduction in the limbic systems (amygdala, hippocampus), paralimbic cortices (insula, cingulated gyrus), superior temporal gyri, and dorsolateral frontal lobes in the left hemisphere predominantly. It should be noted that Peri-Sylvian structures including the speech area and mirror neuron systems are often involved. Clinical symptoms in schizophrenia are characterized by disturbance of the self, and these symptoms may become understandable, if we assume the dysfunctional state of the mirror neuron systems.

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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.

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

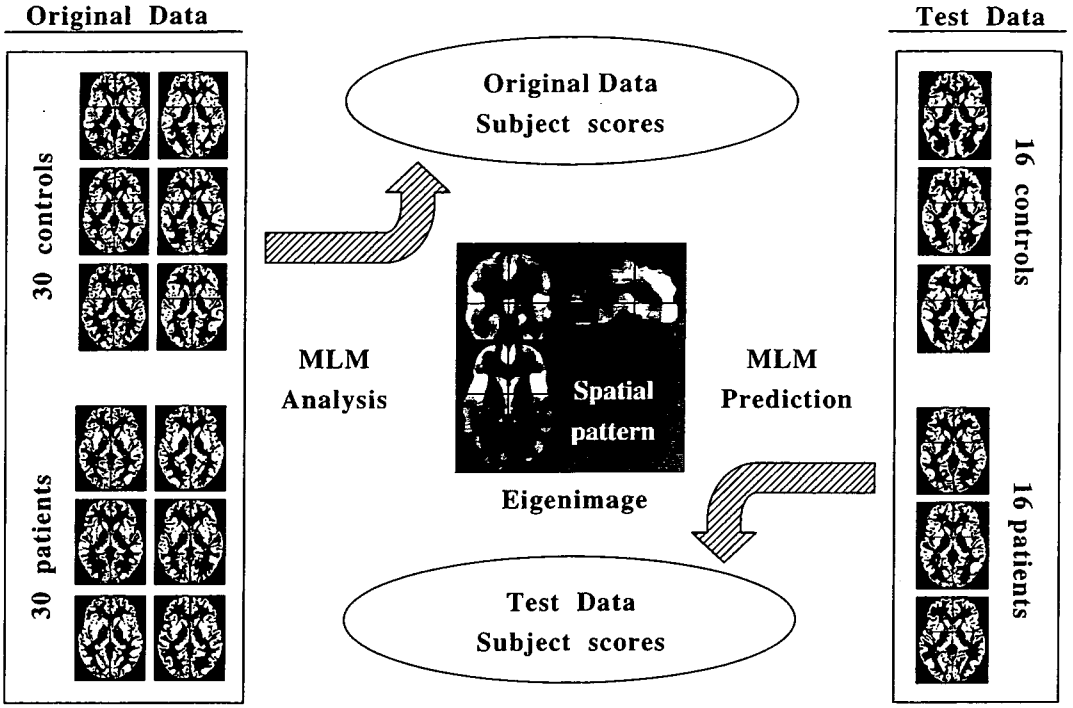

Fig. 1. General scheme of the discriminant function analysis using the VBM and MLM method. An eigenimage and the subject scores were obtained by MLM analysis within the original data. When this eigenimage was used as a predictor of separate data for replication, grouping could be made based on subject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

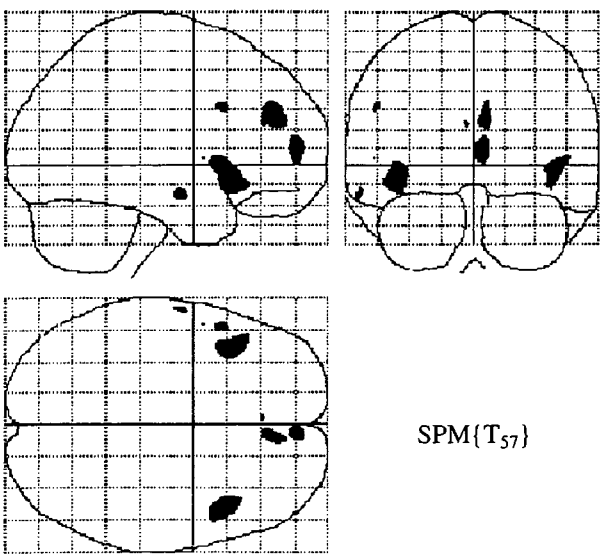

Fig. 2. Distribution of significant voxels with decreased gray matter concentrations in the schizophrenia patients relative to healthy controls. SPM{t} is thresholded at $p<0.05$ corrected for entire volume.

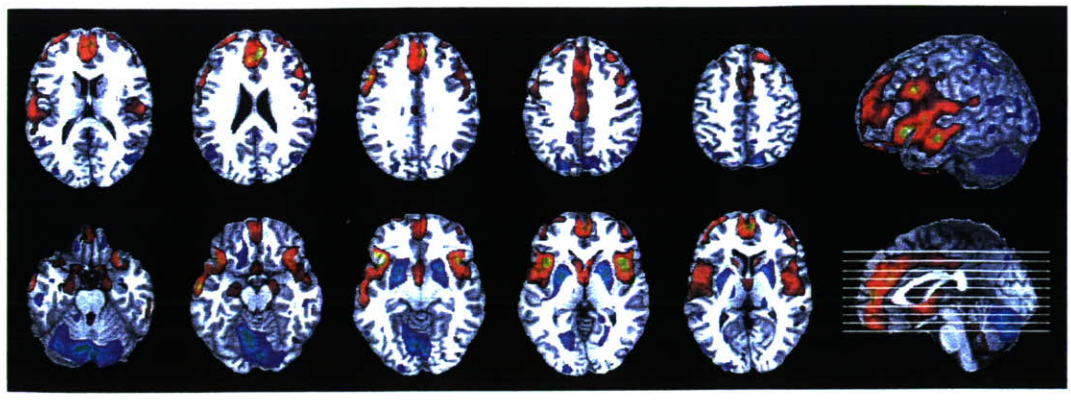

Fig. 3. Eigenimage superimposed on a representative MRI image with the 30% largest loadings for positive (in red) and negative (in blue) loadings.

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

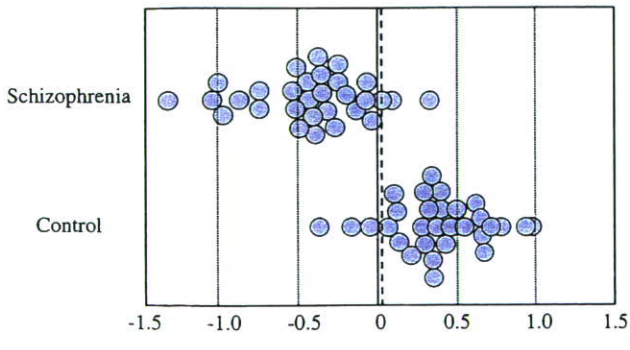

Fig. 4. Expression values of an eigenimage for contrasts between 30 healthy comparison subjects and 30 schizophrenia patients. Dotted line represents demarcation line at 0.036.

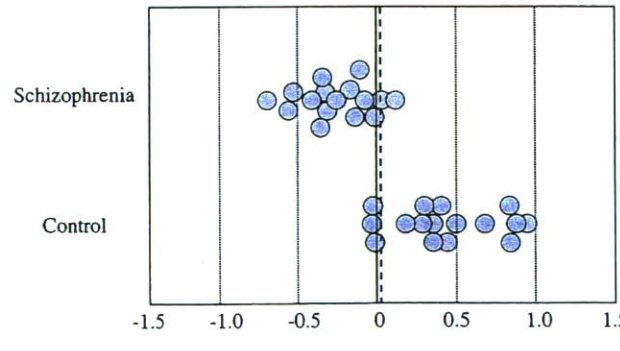

Fig. 5. Post hoc classification of gray matter images of the second cohort with 16 healthy subjects and 16 patients with schizophrenia, based on the eigenimage for contrast between the original comparison subjects and patients. Dotted line represents demarcation line at 0.036.

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.

Keywords: Magnetic resonance imaging; Schizophrenia; Superior temporal gyrus; Medial temporal lobe; Prefrontal cortex; Neurodegeneration

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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