特集 統合失調症の予後改善に向けての新たな戦略

早期介入による予後改善*
DUP短縮に向けて

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Key words

Early intervention, DUP (Duration of Untreated Psychosis), Prognosis, Schizophrenia, Psychosis

はじめに

統合失調症の経過は一様ではなく，その転帰は治療以外のいくつかの要因によっても左右される。発症年齢や性別，居住環境などがそうした転帰予測因子として知られるが，その多くはすでに定まったものであり，介入によって変えることは難しい。一方で精神病未治療期間(Duration of Untreated Psychosis；以下DUP)は，数少ない修正可能な転帰予測因子の1つであり，その点において介入の対象となり得る。早期介入は主としてこのDUPの短縮，さらには発症前からの介入によって，長期的な予後改善を目指すものであるということができる。

本章では統合失調症の早期介入，特にDUP短縮に向けた取り組みに焦点を当て，実際に早期介入が長期的な予後を改善し得るか，その可能性について論じてみたい。

DUP短縮の意義

精神病治療の開始の遅れに注目すべき理由の1つに，未治療の精神病症状がある種の「神経毒性」をもたらす可能性が指摘されている[9,19]。実際に近年の脳画像研究は，脳容積の一部を測定することによって，この可能性を間接的に支持している。Pantelisらは発症の前後で左海馬傍回・紡錘状回，眼窩前頭葉，両側帯状回などに進行性の灰白質減少がみられることを報告している[14]。同様にSunらは発症群で右前頭前野の灰白質減少を[15]，Walterfangらは左前頭後頭束体積の進行性減少を指摘している[17]。こうした縦断的研究はまだ数は少ないながらも，発症前後になんらかの進行性の変化が生じていることがおおむね確認される結果となっている。

DUPとの関連を見た研究の結果からも，同様の変化が未治療期間中に進行している可能性が示唆される。Mallaらは80例の初回エピソード患者をDUPの長短で2群に分け，長期DUPの患者で眼窩前頭葉を中心とする体積減少をより強く認めたとしている[7]。同様にTakahashiらも，長

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表1　フォローアップ時期ごとのDUPと転帰との関係(相関係数の平均値，カッコ内

	ベースライン	6か月	12か月
全症状	−0.020(−0.100〜0.060)	0.362(　0.285〜0.434)	0.282(0.191〜0.368)
抑うつ/不安	0.107(　0.025〜0.188)	0.220(　0.137〜0.300)	0.194(0.094〜0.291)
解体症状	0.020(−0.149〜0.188)	0.200(−0.030〜0.410)	—　　—
陰性症状	0.082(−0.016〜0.179)	0.242(　0.180〜0.302)	0.176(0.106〜0.244)
全般的機能	−0.014(−0.117〜0.090)	0.200(　0.127〜0.271)	0.277(0.165〜0.382)
陽性症状	0.089(−0.041〜0.217)	0.295(　0.234〜0.352)	0.283(0.216〜0.347)
QOL	0.188(　0.081〜0.290)	−0.100(−0.321〜0.132)	0.251(0.157〜0.340)
社会的機能	0.040(−0.085〜0.164)	0.199(　0.008〜0.377)	0.234(0.093〜0.366)

期DUP患者で左上側頭回の体積減少がより強くみられたと報告している[16]。同部位は，初回エピソードの治療後にも進行性の変化がみられるとされており[5]，精神病症状と特異的に関連する所見として注目される。

こうした所見はDUP短縮の理論的背景をある程度裏付けるものであるが，臨床的により強調されるのは，未治療状態を放置することの非合理性である。未治療状態が長く放置されれば，本人あるいは周囲にとって不必要な苦痛が持続され，社会的にも孤立を深めるなど，長期的な社会予後をより不良にすると考えられる。早期介入の効果を定量化していく試みはまだ始められたばかりであるが，このような臨床的観点から，DUP短縮にはすでに明らかに正当な理由があると多くの臨床家は考えている。

DUPと転帰との関連

DUPは精神病発症から治療開始までの精神病症状の持続期間と定義されるが，実際の正確な測定にはしばしばいくつかの困難が伴う。第一に，精神病の発症時点は後方視的な情報に頼らざるを得ないため，後方視的想起に伴うバイアス(不正確な記憶，否認や認知面での障害による影響)が避けられない。第二に，精神病体験が主観的現象であり，客観的に明白でない点が挙げられる。家族による発症時点の推定は，患者本人からの報告に比べ，しばしば明らかに遅れることが確認されている[12]。

加えて，研究間での測定に関する不一致も問題となり得る。精神病の発症の定義は各研究でさまざまに異なり，なかには陽性症状だけでなく解体症状をその基準に組み込むなど，何を「精神病性」と定めるかはときに恣意的でさえある。治療の開始についても同様であり，抗精神病薬の投与開始から初回入院まで，その定義は研究間で一致していない。特に治療開始を初回入院とした場合には，その対象は入院患者に限られることになり，サンプルの偏りも問題となる。さらに多くの研究では標準化された評価尺度を用いておらず，信頼に足るデータが得られているとは言い難い面もある。

こうしたDUPの評価に関するいくつかの問題を考慮したとしても，DUPと転帰との関連は比較的堅牢であるとされている。Marshallらは初発例を前方視的に追跡した研究のレビューを行い，フォローアップ6，12か月後で，長期DUP群と短期DUP群の間に症状，機能，QOL(quality of life)などの転帰に関する有意差を示さなかったのは21の研究中4つのみであり，そのうち3つは少数の被験者によるものであったと報告した[3]。これらの相関は初回評価時には明らかでない場合が多く，主として治療が継続された後に出現していた(表1)。上述したように各研究間でDUP測定方法には相違がみられたが，初回評価時に認められたDUPの長短による転帰の差異のエフェクトサイズの違いが，フォローアップ時には消失することが確認されている。また転帰への交絡因子となる可能性のある病前適応に関しても，重回帰分析による詳細な検討を行い，病前適

は95%信頼区間)

24か月	
—	—
—	—
—	—
−0.110(−0.259〜0.044)	
0.280(　0.045〜0.486)	
0.170(　0.017〜0.315)	
0.200(　0.048〜0.343)	
0.190(−0.079〜0.433)	

応が転帰に影響を及ぼす可能性を支持する結果は得られなかったとしている。このレビュー内には含まれていないものの，わが国における唯一のDUPと転帰との関連を見たYamazawaらの研究でも，同様の結果が示されている[20]。

ケアへの経路と援助希求

DUPは主として2つのコンポーネント，すなわち症状出現から受診までと受診から適切な治療開始までの期間に分けることができるとされている。したがってDUPの短縮に向けた取り組みも，この2つのコンポーネントに対して行われると考えられる。

第一のコンポーネント，すなわち症状出現から受診までの期間を短縮するためには，まずメンタルヘルスに対する一般の認識をより適切な形に高めることが重要である。この「メンタルヘルス・リテラシー」のコミュニティにおける普及啓発が，本人あるいは家族の援助希求行動に直結すると考えられている。事実，いくつかのメンタルヘルス・リテラシーの実態調査とその介入効果に関する研究から，それを支持する結果が得られている。

メンタルヘルス・リテラシーの実態を把握する調査によれば，精神病性障害に対する認識は期待されている水準よりも低く，しかも各国によって差があることが判明している。Jormらは一般住民における精神病性障害の認識率を評価する研究を日豪共同で行い，オーストラリアでは41%が正しい認識を示したのに対し，日本では同様の調査で17%と低い割合であったと報告している[4]。同研究ではさらに，精神病性障害に対する医療専門家の有用性評価について認識調査を行い，その結果は援助希求の対象が各地域の医療・保健システムに依存する可能性を示している。たとえば，オーストラリアでは，精神病性障害の支援に有用な専門職として77%がGP(general practitioner；家庭医)を挙げているが，日本ではその割合は19%に過ぎない。一方，両国に共通していえることはその有効な支援の提供先としてカウンセラーの存在が大きく(いずれも85%以上)，精神科医よりも期待度が高い。このことは精神病性障害が医学的な問題であるというよりも，生活上の問題，ある種のストレスの反応として一般市民の間で考えられていることを示しているともいえる。

こうした有効と期待される支援先に行き着いたとしても，適切な治療が開始されないこともしばしばあり，それが前述した第二のコンポーネントに相当する。ケアへの経路に関するいくつかの調査では，初めの専門家への相談から適切なケアに至るまで平均で3〜5回の専門家への接触があったと報告されており，その回数は治療の遅れに関連していると考えられている[1,6]。なかでも最初にGPに接触する頻度は欧米諸国では35〜45%であるとされており，ケアの経路におけるいくつかのポイントにおいて少なくとも50%がGPに接触するという報告もある[3]。したがって一見するとGPへの接触が治療の遅れに関与するととらえられがちだが，必ずしもGPのみが律速段階であるとは限らない。むしろ発症前にメンタルヘルス専門家に接触した場合のほうが，適切な診断や治療が行われるのがより遅くなるとNormanらは指摘しており[13]，しかるべき適切なアセスメントがメンタルヘルスサービスにおいて十分に行われていない可能性が示唆される。

DUP短縮に向けた取り組み

このような実態調査に基づいて，実際に治療の遅れを減らすことを試みた実証研究がいくつかなされている。

表2 Compass Strategyキャンペーンの1例(文献17)より筆者訳)

・新聞広告スクリプト
若者の4人に1人が，精神病などのメンタルヘルスの問題に直面しています。
次に挙げるのは，そうした問題のサインかもしれません。
・仕事や勉強がはかどらない
・家族や友人とうまく付き合うことができない
・そのサインは他の人は見たり聞いたりすることができない
・現実的ではない奇妙な，普通でない考えにとりつかれる
ケアを早期に受けることが，問題解決の第一歩かもしれません。その方法を見つけ出すために，1300にお電話を，またはhttp://www.getontop.orgまで。

・映画広告スクリプト
毎年，4人に1人の若者が，なんらかのメンタルヘルスの問題を経験しています。
それらは無視すればするほど，対処できなくなってしまいます。
しかし早い段階からケアを受けることによって，早期に回復することができるでしょう。
メンタルヘルスの問題について詳しく知りたい方は，1300にまずお電話ください。
悩む前に，行動を。

オーストラリアで2001年から2年間にわたって行われたCompass Strategyは，コミュニティにおけるメンタルヘルス・リテラシーの改善を目的とした介入プログラムである[18]。このプログラムは，メルボルンを中心とした地域を介入群とコントロール群の2つに分けて行われた。メンタルヘルスに対する認識を促進するキャンペーンは「悩む前に行動を(get on top of it, before it gets on top of you)」というキー・スローガンのもと，映画，新聞，雑誌，ウェブサイトなどのメディアを通じてメッセージを発し続けた(1例を表2に示す)。結果として介入地域ではコントロール地域に比較して，精神疾患や自殺リスクへの認知，援助希求へのバリアの減少，うつ病の援助希求の増加などが有意に認められた。

同様の介入はカナダ，オンタリオでも行われている。このプログラムでは早期介入サービスの立ち上げとともに，それを関連機関に周知させる一方，広くコミュニティに対してもパンフレットやポスター，映画広告などを通じたキャンペーンを行った[8]。しかしながら介入プログラムの前後でDUPの中央値には，有意な改善を認めなかった(前：21.9週，後：24.3週)。この結果については，介入プログラムが最近発症したケースの治療の遅れを減らすことに成功した一方で，治療されずに放置されていたケースを再発見したことが，その理由として推測されている。

この2つのプログラムをさらに進めたものが，スカンジナビアで行われたTIPS『"Tidlig Intervention i Psychose"(ノルウェー語で「精神病早期介入」の意)』プログラムである。ノルウェーのRogaland州にある2つの保健地区で大規模な介入プログラムを行い，一方ノルウェーのOslo州とデンマークのRoskilde州の2つの保健地区が非介入の対照地域とされた[10]。介入プログラムでは，新聞やラジオ，映画，パンフレット，Tシャツ，自動車ステッカーに至るまで，さまざまなメディアを通じてコミュニティキャンペーンが行われた。さらに，GPやスクールカウンセラー，ソーシャルワーカーなどへの情報教育や普及啓発，また利便性の高い早期発見チームの設立を同時に行った。その結果，DUPの中央値が介入地域で有意に短縮され(5週対16週)，全般的機能もインテーク時からその後3か月後まで介入地域のほうが有意に高い値を示しており，プロジェクトの推進が早期発見に一定の効果があったことを示唆している。

シンガポールで行われた国家的プログラムであるEPIP (Early Psychosis Intervention Programme)も，同様に肯定的な介入効果を示して

いる[2]。TIPSと同様にEPIPでも，さまざまなメディアを経由したコミュニティにおける普及啓発と，GPやスクールカウンセラーを対象とした情報提供が行われ，さらにプライマリケアサービスのネットワークの構築も行った。結果としてDUPの中央値は12か月から4か月に有意に減少し，警察からの照会が減った一方で本人や家族からの照会が増えるという，ケアの経路における良好な変化も認められた。

このようなDUP短縮に向けた取り組みはすでにそれ自体意義深い研究の1つであるが，その結果をさらに長期的にフォローすることによって，DUPと転帰とのより正確な関連性を得ることが可能となると考えられる。

おわりに—わが国におけるDUP短縮の可能性

以上見てきたように，DUPはその生成過程の複雑さや定義の問題はあるにしても，長期予後とは一定の関連性が認められており，なおかつ介入によって短縮可能であることが示唆される。DUPを短縮する取り組みが長期予後を改善するかについては，厳密には今後のフォローアップ研究の成果を待つ必要があるが，DUPと長期転帰の関連性を考えればDUP短縮による予後改善の可能性はおおむね支持されているといってよいであろう。したがってわが国においても同様の取り組みを推進していく必要があると考えるが，同時にいくつかの課題を克服していく必要がある。

前述の日豪共同研究が示したように，わが国において精神病に対する正しい認識は一般に低く，有効なケアのネットワークも十分に整備されていない。たとえ受診を選択した場合でも，通常精神科医が窓口になることが多く，そこでは正確な診断や治療を開始するだけの時間的余裕も限られている。結果的に適切なケアがなされないまま，後に強制的な手段でようやく治療が開始されるというケースも少なくない。早期支援の窓口は大学病院を中心に増加傾向にあるが[11]，そうした活動に加えて，かかりつけ医やスクールカウンセラー，学校保健医などを含めたプライマリケアのネットワークを構築することが，わが国においては喫緊の課題といえる。

また援助希求のデータが明らかにしているように，適切なケアに至るまで複数回の専門家への接触がみられている。これは，抱えている問題の本質を適切にアセスメントする機能がメンタルヘルスサービスに希薄であることを示すのと同時に，その問題に関連する主観的な苦悩や周囲への影響が，病初期であっても決して小さくないことを示している。援助希求のバリアが諸外国に比べ高く，ひきこもりなどの孤立を容易に生じやすいわが国においては，こうした問題に適切に対処する当事者・家族志向の相談サービスの充実を，まずは期待したいと思う。

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MEDICAL BOOK INFORMATION ——— 医学書院

＜神経心理学コレクション＞

脳を繙く 歴史でみる認知神経科学

HISTORY OF COGNITIVE NEUROSCIENCE

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認知神経科学について「歴史」を切り口に解説するもの。認知（記憶など）、言語、運動といった神経心理学領域で扱われる一通りのテーマについて、過去から現在までの歴史的な流れが押さえられるとともに、用語や人名などを網羅的に収載しているため、教科書的・辞書的に使うことも可能。神経内科医・精神科医はもちろん、初学者やコメディカルが神経心理学領域を理解するためのサブテキストとしても有用な1冊。

Effect of Tandospirone on Mismatch Negativity and Cognitive Performance in Schizophrenia
A Case Report

To the Editors:

Disturbances of cognitive function, evaluated by neurophysiological[1–3] and psychological[4] measures, have been shown to predict outcome in patients with schizophrenia. Mismatch negativity (MMN) is an event-related potential (ERP) generated in response to occasional variations of acoustic stimuli and is suggested to reflect preattentive cognitive operations.[5] Specifically, reduced MMN amplitudes in response to frequent-deviant stimuli have been associated with the pathophysiology of schizophrenia, including decreased gray matter volumes of the prefrontal cortex and superior temporal gyrus.[6]

A limited number of studies report the ability of dopamine,[7] serotonin (5-HT),[7–11] and *N*-methyl-D-aspartate acid (NMDA)[9] transmissions to modulate MMN in healthy human subjects. Here, we report a case of schizophrenia in which adjunctive use of tandospirone, a 5-HT_{1A} partial agonist and anxiolytic,[12,13] was effective for enhancing MMN and improving cognitive performance.

CASE REPORT

The patient is a 37-year-old woman meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for schizophrenia. She graduated from a mainstream high school and entered a university. At age 20, she experienced auditory hallucinations, delusion of persecution, and emotional instability and was admitted to a local psychiatric hospital immediately after the police spotted her wandering around in the rain. After discharge, she gave up studying and took a part time job, which did not last long because of social withdrawal despite treatment with haloperidol (up to 6 mg/d) and sulpiride (up to 150 mg/d). At age 35, she was rehospitalized because of severe auditory hallucinations, delusion of persecution, thought disturbance, and stupor. Switching to monotherapy with olanzapine at 20 mg/d was effective in treating these symptoms, and the patient was discharged after a 3-month hospitalization.

Although her general psychiatric conditions remained relatively well, she occasionally reported anxiety, which became more frequent and severe when she began to take care of her nephew whose mother had obtained a job. At this time, the patient was able to help the household of her brother's family, which she lived with, but was not motivated enough to go out by herself. For anxiolytic purpose, tandospirone, 30 mg/d as initial dose, was added, which was titrated to 60 mg/d (recommended maximum dose) during the initial month, because of the insufficient effect of the lower dose. The dose of olanzapine was unchanged. By 3 months after the start of tandospirone, her anxiety symptoms almost disappeared, and remained so at 6 months. By this time, she gained motivation to shop at a grocery store by herself and pursue her favorite hobbies (embroidery and others).

Electroencephalograms (EEG) were recorded before the start of tandospirone and 3 and 6 months thereafter, according to a regimen previously reported.[14] Mismatch negativity, in response to frequency-deviant tones, was measured with an oddball paradigm. Auditory stimuli were delivered binaurally through headphones with interstimulus intervals of 0.5 second. Deviant tones of 1500 Hz were randomly presented in a series of standard tones of 1000 Hz,

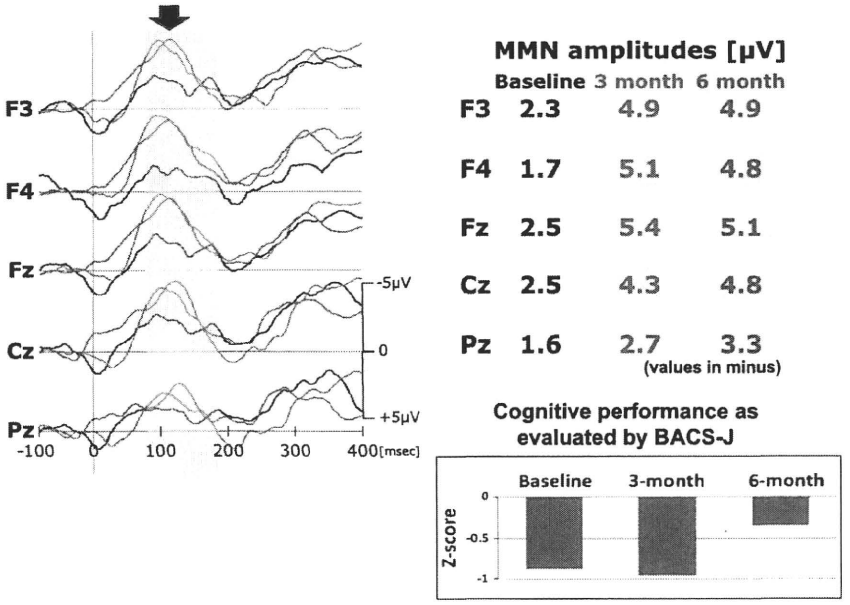

FIGURE 1. Effect of adjunctive use of tandospirone, a 5-HT_{1A} partial agonist, on MMN in a patient with schizophrenia receiving olanzapine. Mismatch negativity amplitudes (indicated by an arrow) in response to frequent-deviant stimuli were increased both at 3 and 6 months after the addition of tandospirone. Inset: cognitive performance, as evaluated by the Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J) composite score, was improved at 6 months compared with baseline.

with the presentation probability of 0.1 for the deviant tones. During the recordings, subjects were requested to watch animation. All electrodes were referred to the average amplitude of ear electrodes (bandwidth, 0.16–120 Hz; notch filter, 60 Hz). Electrode impedance was less than 10 kΩ. Data were collected with a sampling rate of 500 Hz. Averaging of ERP waves and related procedures were performed using EPLYZER II software (Kissei Comtec, Co Ltd, Nagano, Japan). The epoch was 600 milliseconds, including a 100- millisecond prestimulus baseline. Neuropsychological assessment was conducted with the Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J)[15] at the electroencephalogram measurement. Alternate forms, where appropriate, were used at reassessments. Written informed consent was obtained for these clinical evaluations.

As shown in Figure 1, MMN amplitudes were increased as early as 3 months from the start of augmentation therapy with tandospirone and remained so at 6 months. The BACS-J composite scores (in *Z*-score) at baseline, 3 months, and 6 months were −0.88, −0.95, and −0.32, respectively (Fig. 1, inset), suggesting improved performance after a 6-month adjunctive treatment.

DISCUSSION

To our knowledge, these findings provide the first evidence for the ability of 5-HT_{1A} partial agonists to improve MMN in subjects with schizophrenia. So far, only a limited number of neurochemical manipulations have been reported to enhance MMN in healthy volunteers, for example, 5-HT reuptake inhibitors,[10,11] tryptophan depletion,[8] and nicotinic receptor stimulation,[5] whereas *N*-acetyl-cysteine, a glutathione precursor, has been shown to enhance MMN in patients with schizophrenia.[16] Whether increased or decreased serotonergic tones enhance MMN amplitudes has been controversial,[7,8,10,11] suggesting a role for specific 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A} receptors, in the modulation of MMN. It is likely that the deficits in MMN before the start of tandospirone treatment were due to chronicity of the illness (>17 years), rather than a possible influence of olanzapine, for example, actions on 5-HT_{2A} receptors.

The addition of tandospirone was associated with a favorable effect on behavioral performance as evaluated by neuropsychological assessments, consistent with previous reports that 5-HT_{1A} agonists, for example, tandospirone,[12,13] buspirone,[17] and perospirone,[14,18] ameliorated cognitive deficits related to frontal lobe function in subjects with schizophrenia. It is noteworthy that the change in MMN waveforms preceded the improvement of behavioral performance during treatment (Fig. 1). This divergence in time suggests that some of the electrophysiological signals reflecting preattentive cognitive process may be able to predict treatment efficacy in neuropsychological performance.

The effect of 5-HT_{1A} agonism on MMN may be mediated by its influence on glutamatergic and, possibly, GABAergic function. This assumption is based on observations that blockade of NMDA receptors reduces MMN[9,19] and that 8-OH-DPAT, a 5-HT_{1A} agonist, modulates cortical activity through 5-HT_{1A} receptors located on GABAergic interneurons and those on pyramidal neurons.[20] Further study is needed to confirm the potential benefit of agents acting on 5-HT_{1A} receptors for improving MMN and other components of ERPs in people with schizophrenia.

AUTHOR DISCLOSURE INFORMATION

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Volume reduction and altered sulco-gyral pattern of the orbitofrontal cortex in first-episode schizophrenia

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ABSTRACT

Background: Although clinical and neuropsychological findings have implicated functional deficits of the orbitofrontal cortex (OFC) in schizophrenia, structural magnetic resonance imaging (MRI) studies of this region have yielded inconsistent findings. In addition, it remains elusive whether the OFC morphology in first-episode patients is related to their clinical features.
Method: MR images were acquired from 42 (24 males, 18 females) first-episode schizophrenia patients and 35 (20 males, 15 females) age-, gender-, and parental socio-economic status (SES)-matched healthy subjects. The OFC sub-regions (orbital gyrus and straight gyrus) were measured on contiguous 1-mm-thick coronal slices. The OFC sulco-gyral pattern was also evaluated for each subject. Furthermore, the relationships between OFC morphology and clinical measures were examined.
Results: The volumes of the bilateral orbital gyri were significantly reduced in schizophrenia patients compared with healthy subjects, whereas the volumes of the straight gyri did not show differences between the groups. Among the schizophrenia patients, the volume of the left orbital gyrus was inversely correlated with their SES and illness duration. The OFC sulco-gyral patterns were significantly different between the patients and controls in the right hemisphere.
Conclusion: This study demonstrated morphologic abnormalities of the OFC in first-episode schizophrenia patients, which may have reflected neurodevelopmental aberrations and neurodegenerative changes during the first episode of the illness. Our findings also suggest that such brain structural changes are related to the social dysfunction observed in schizophrenia.
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1. Introduction

The orbitofrontal cortex (OFC), a part of the prefrontal cortex (PFC) located in the ventral surface of the frontal lobe, is a core component of the social brain network (Kringelbach, 2005; Rolls and Grabenhorst, 2008). The OFC, which has mutual connections with the amygdala, cingulate gyrus, dorsolateral prefrontal cortex (DLPFC), and hypothalamus (Carmichael and Price, 1995a,b; Rempel-Clower and Barbas, 1998; Öngür and Price, 2000), is thought to modulate human

Abbreviations: ANCOVA, Analysis of covariance; ANOVA, Analysis of variance; BPRS, Brief Psychiatric Rating Scale; DUP, Duration of untreated psychosis; ICC, Intraclass correlation coefficients; ICD-10, International Classification of Diseases, 10th edition; ICV, Intracranial volume; JART, Japanese version of the National Adult Reading Test; MRI, Magnetic resonance imaging; OFC, Orbitofrontal cortex; ROI, Region of interest; PFC, Prefrontal cortex; SES, Socio-economic status; VBM, Voxel-based morphometry.

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behavior through a stimulus-reinforcer association learning process, and it is also involved in various cognitive functions such as emotional processing and decision making ability (Haas, 2001; Kringelbach, 2005; Murray et al., 2007; Rolls and Grabenhorst, 2008). Individuals with OFC lesions have been reported to suffer social dysfunction due to impairment of decision making, lack of affects, inappropriate behavior, and irresponsibility, which are often observed in patients with schizophrenia (Eslinger and Damasio, 1985; Anderson et al., 1999; Blair and Cipolotti, 2000; Hornak et al., 2003).

Functional abnormalities of the OFC in schizophrenia have been demonstrated in neuropsychological studies using decision making (Shurman et al., 2005; Kester et al., 2006; Lee et al., 2007; Martino et al., 2007; Nakamura et al., 2008; Yip et al., 2009) and reversal learning (Waltz and Gold, 2007) tasks. Several functional neuroimaging studies have implicated dysfunctional neural networks including the OFC in emotional processing deficits (Dolan and Fullam, 2009; Reske et al., 2009) as well as in positive symptomatology (Parellada et al., 2008) of schizophrenia. However, structural magnetic resonance imaging (MRI) studies of schizophrenia have reported variable findings in this region, with decreased (Gur et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Kawasaki et al., 2004; Suzuki et al., 2005; Kim et al., 2007; Nakamura et al., 2008; Venkatasubramanian et al., 2008), normal (Baaré et al., 1999; Crespo-Facorro et al., 2000; Yamasue et al., 2004; Shad et al., 2006; Sapara et al., 2007), and even increased (Lacerda et al., 2007) volumes compared with healthy control subjects. The OFC volume deficits in schizophrenia have been associated with several clinical variables such as illness duration (Nakamura et al., 2008) and the severity of both positive (Nakamura et al., 2008) and negative (Baaré et al., 1999; Gur et al., 2000; Koutsouleris et al., 2007) symptoms, but others did not show these relationships (e.g., Suzuki et al., 2005; Kim et al., 2007; Venkatasubramanian et al., 2008). These inconsistencies between reports could be partly related to methodological differences, including different imaging techniques [e.g., region-of-interest (ROI) based or voxel-based, differences in anatomical ROI boundaries] and sample characteristics (e.g., first-episode versus chronic patients, medications status, and symptom severity). Interestingly, recent longitudinal MRI studies have demonstrated progressive gray matter reduction of the OFC during the earliest phases of schizophrenia (Pantelis et al., 2003; Borgwardt et al., 2008), suggesting a neurodegenerative pathology of the illness (Pantelis et al., 2005; Wood et al., 2008). However, most MRI studies of the OFC in schizophrenia have examined chronic patients who had already been exposed to several confounding factors such as antipsychotic medication or chronicity of the illness. In addition, only one ROI-based MRI study has investigated the OFC subregions (i.e., orbital gyrus and straight gyrus) in first-episode schizophrenia (Crespo-Facorro et al., 2000) and the relationship between these subregional volumes and the clinical features seen at the first-episode of the illness remains largely unknown.

The structural heterogeneity of the OFC sulco-gyral pattern is also an important consideration, since altered gross cortical folding patterns have been reported in schizophrenia, possibly reflecting a disturbance in neurodevelopment (Yücel et al., 2002; Le Provost et al., 2003; Fujiwara et al., 2007; Nakamura et al., 2007a, 2008). As for the high inter-individual structural variability of the OFC, Chiavaras and Petrides (2000) classified its sulco-gyral pattern into three types (Types I, II, and III) using the variations of the "H-shaped" sulcus. Based on this method, Nakamura et al. (2007a) demonstrated a significant difference in the distribution of the OFC sulco-gyral pattern between chronically medicated schizophrenia patients and healthy subjects, suggesting that the OFC deficits in schizophrenia at least partly reflect neurodevelopmental abnormalities. Furthermore, they demonstrated that the rarest form, Type III, was associated with poor socioeconomic status, poor cognitive functioning, and severe symptoms in schizophrenia. To the best of our knowledge, however, no MRI study has investigated the OFC sulco-gyral pattern in first-episode schizophrenia patients.

In this study, we used MRI to examine the OFC subregional volume and sulco-gyral pattern in patients with first-episode schizophrenia and matched healthy subjects. On the basis of previous neuroimaging findings, we hypothesized that (1) the OFC volume would be reduced even in first-episode schizophrenia patients compared with healthy subjects and that (2) the distribution of sulco-gyral patterns in patients would be different from that of the controls. We also explored the relationship between OFC morphology and clinical variables in schizophrenia.

2. Methods

2.1. Subjects

Forty-two patients (24 males, 18 females) with first-episode schizophrenia were recruited from the inpatient population at the Tokyo Metropolitan Matsuzawa Hospital. Inclusion criteria were (1) first psychiatric hospitalization, (2) younger than 45 years old, (3) currently psychotic as reflected by the presence of at least one "positive" symptom, and (4) a duration of psychosis of at least one month. Diagnoses were made according to the ICD-10 research criteria for schizophrenia (World Health Organization, 1993), based on direct interview as well as medical chart review. At least two experienced psychiatrists separately examined the patients within two weeks of admission and diagnostic consensus was confirmed. Furthermore, we checked the diagnostic stability of all the patients included in the present study during the follow-up periods (1 to 5 years) after first admission. All but three males were right-handed. All patients had already been treated with neuroleptics at the time of scanning (medication duration median = 57.4 days). Twenty patients were treated with atypical antipsychotics alone, and 22 patients received both typical and atypical antipsychotics. Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962).

The control subjects consisted of 35 healthy volunteers (20 males, 15 females) who were recruited from the hospital staff and college students. All of the control subjects were right-handed. Control subjects with a personal or family history of psychiatric illness were excluded.

The premorbid IQ for schizophrenia patients and the present IQ for control subjects were estimated using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Matsuoka and Kim, 2006; Uetsuki et al., 2007).

The subjects' socio-economic status (SES) as well as parental SES was assessed using the Hollingshead's Index (Hollingshead, 1975). The educational level was scored on a seven-point scale according to the completed years of school, and occupation was coded on a nine-point scale. Greater score indicates higher educational/occupational level. When a patient was on a leave of absence due to the onset of psychosis, the occupational factor was scored by the current job unless he/she had quit it. The SES score was calculated by multiplying the scale value for education by a weight of 3 and the scale value for occupation by a weight of 5. Then the SES category (1 to 5) was assigned according to the SES score. A smaller numerical value indicates a higher social position.

Table 1 shows the demographic and clinical data of the subjects. The two groups (i.e., schizophrenia patients and control subjects) were matched for age, gender, and parental SES. The control subjects had a higher SES [ANOVA, $F=33.17$ ($df=1,72$), $p<0.001$] and a higher estimated IQ [ANOVA, $F=8.02(df=1,72)$, $p=0.006$].

All subjects were physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or significant alcohol or substance abuse disorder. All subjects participated in this study after providing written informed consent. This study was approved by the Committee on Medical Ethics of Tokyo Metropolitan Matsuzawa Hospital.

2.2. Magnetic resonance imaging procedures

MR images were obtained using a Philips Intera 1.5-T scanner (Philips Medical Systems, Best, The Netherlands) with a three-dimensional sequence yielding 192 contiguous T1-weighted slices of 1.0-mm thickness in the axial plane. The imaging parameters were as follows: repetition time = 21 ms, echo time = 9.2 ms, flip angle = 30°, field of view = 256 mm, matrix size = 256 × 256 pixels, voxel size = 1.0 × 1.0 × 1.0 mm^3. The intensity non-uniformity in MR data was corrected by the non-parametric non-uniform intensity normalization (N3) method (Sled et al., 1998).

Detailed procedures for the image volumetric analysis have been described elsewhere (Takayanagi et al., 2010). Briefly, on a UNIX workstation (Silicon Graphics, Inc., Mountain View, CA), the image data were randomly coded and analyzed with the Dr. View 5.3 software package (Asahi Kasei Joho System, Tokyo, Japan). Head tilt during the scanning was corrected in three dimensions. Brain images were then reconstructed into entire contiguous coronal images of 1-mm thickness vertical to the anterior commissure-posterior commissure line. The signal-intensity histogram distributions from the T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into gray matter, white matter, and cerebrospinal fluid (CSF) according to the Alpert algorithm (Alpert et al., 1996). Finally, obtained gray matter images were carefully inspected and corrected manually if a segmentation error was found, although we employed a signal intensity-inhomogeneity correction (N3) method.

2.3. Brain volumetric measurements

2.3.1. Orbitofrontal cortex volume measurements

Gray matter volumes of the orbital and straight gyri were measured in consecutive 1-mm thick coronal slices. As the lateral orbital sulcus (the lateral ramus of the "H-shaped" sulcus) and olfactory sulcus are less variable than other OFC sulci, we employed these two stably observed sulci as anatomical boundaries of the regions of interest (ROI), as was the case in a recent study (Nakamura et al., 2008). The boundaries of each ROI were defined as described in Table 2. Fig. 1 presents the delineation of both cortical regions.

2.3.2. Intracranial volume (ICV) measurements

For following statistical analyses, ICV was measured to correct for differences in head size. Brain images were reformatted into consecutive 5-mm-thick sagittal slices with each voxel as $1\times1\times5\ mm^3$. The intracranial cavity was manually traced in each slice, using the anatomical landmarks shown by Eritaia et al. (2000).

2.4. Identification of the OFC sulco-gyral pattern

We used the OFC sulco-gyral pattern classification method demonstrated by Chiavaras and Petrides (2000). Briefly, OFC sulco-gyral patterns were classified into the following three types according to the continuity of the "H-shaped" sulcus consisting of the medial orbital sulcus, transverse orbital sulcus, and lateral orbital sulcus. In type I, the medial orbital

Table 1
Demographic and clinical characteristics of the subjects.

	Schizophrenia patients		Control subjects		Analysis of variance			
	Male	Female	Male	Female	Diagnosis		Gender	
	($n=24$)	($n=18$)	($n=20$)	($n=15$)	F	p	F	p
Age (years)	28.6 ± 5.9	29.7 ± 5.7	30.6 ± 5.5	28.5 ± 4.5	0.11	0.741	0.16	0.688
Handedness (number of right handed subjects)	21	18	20	15				
Socio-economic status	2.7 ± 1.2	2.9 ± 1.1	1.7 ± 0.5	1.6 ± 0.5	33.17	<0.001	0.07	0.800
Parental socio-economic status	2.4 ± 0.9	2.7 ± 0.8	2.3 ± 0.7	2.3 ± 0.6	1.35	0.249	1.24	0.270
Estimated IQ[a]	102.6 ± 9.8	102.1 ± 7.7	108.9 ± 7.2	107.2 ± 9.0	8.02	0.006	0.81	0.776
Duration of untreated psychosis (months)	7.7 ± 10.3	9.9 ± 13.6						
Duration of illness (months)	10.5 ± 12.0	13.7 ± 13.1						
Duration of medication (days)	41.8 ± 67.2	79.5 ± 71.9						
Medication (mg/day, chlorpromazine equiv.)	1007.1 ± 516.7	901.3 ± 465.9						
Total BPRS score	40.7 ± 11.1	37.9 ± 9.5						

BPRS, Brief Psychiatric Rating Scale.
[a] Estimated IQ was measured using the shortened version of the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Uetsuki et al., 2007).

Table 2
Anatomical boundaries of the regions of interest.

Region	Anatomical landmark
Orbital gyrus	
Anterior border	Frontomarginal sulcus
Lateral border, anterior part[a]	Frontomarginal sulcus
Lateral border, intermediate part	Lateral orbital sulcus (lateral ramus of "H-shaped" sulcus)
Lateral border, posterior part[a]	Inferior circular sulcus
Medial border, anterior part	Superior rostral sulcus
Medial border, intermediate and posterior part	Olfactory sulcus
Posterior border	Most posterior slice in which inferior circular sulcus was clearly seen
Straight gyrus	
Anterior border	Most anterior slice in which olfactory sulcus was clearly seen
Lateral border	Olfactory sulcus
Medial border	The nearest point on the midline from the deepest point of the olfactory sulcus
Posterior border	Olfactory trigone

[a] When two sulci were seen in the same slice, the lateral orbital sulcus was used as the lateral border.

sulcus was clearly interrupted between the rostral and caudal portions while other sulci were connected. In Type II, the H-shaped sulcus was uninterrupted. In Type III, the rostral and caudal portions of both the medial orbital sulcus and lateral orbital sulcus were interrupted (Fig. 2. Also see figures of Chiavaras and Petrides, 2000).

2.5. Reliability

All ROI measurements and the OFC sulco-gyral pattern classification were carried out by one rater (Y.T.) without knowledge of the subjects' gender or diagnosis. To evaluate the inter-rater reliability, a second rater (N.M.) blinded to the subjects' identity performed both the ROI delineation and sulco-gyral pattern classification. The intra- and inter-rater reliability for ROI measurements were established by measuring all regions in five randomly selected subjects. The intra- and inter-rater intraclass correlation coefficients (ICC) for ROI measurements ranged from 0.97 to 0.99 and from 0.91 to 0.96, respectively. To assess the intra- and inter-rater reliability for the OFC sulco-gyral pattern identification, 25 randomly chosen cases were evaluated (50 hemispheres). The intra- and inter-rater ICC (kappa) for the OFC sulco-gyral pattern classification were 0.93 and 0.83, respectively.

2.6. Statistical analysis

All statistical analyses were performed using the STATISTICA 06J software package (Statsoft, Tulsa, OK). Statistical differences in the regional volumetric measures were analyzed for each ROI, using repeated measures of analysis of covariance (ANCOVA) with ICV and age as covariates, group (patients, controls) and gender (male, female) as between-subject factors, and hemisphere (left, right) as a within-subject factor. For the comparison of ICV, only age was treated as a covariate. Group differences in sulco-gyral pattern distribution were evaluated using the Chi-square test. One-way ANCOVA using the OFC sulco-gyral pattern (Types I–III) as a between-subject factor was conducted for each hemisphere in order to investigate regional volumetric changes associated with different sulcogyral patterns. The relationships between sulco-gyral pattern and clinical parameters (e.g., SES, illness duration, BPRS scores) were analyzed for each hemisphere using ANOVA with the OFC sulco-gyral pattern (Types I–III) as a between-subject factor. Post hoc Tukey's honestly significant difference tests were used to follow up significant main effects or interactions. The relationships between the ROI volumes and estimated IQ, total and subscale BPRS scores, the medication dosage and the exact SES scores were examined with Pearson's r on the basis of normal distribution of these variables (Kolmogorov–Smirnov test), whereas Spearman's rho was used for analyses involving duration of untreated psychosis, duration of illness and duration of medication due to their skewed distribution, or the SES category (ranged 1 to 5), due to the ordinal nature of the data. To control for differences in head size, relative volume (regional volume/ICV) was used for correlation analyses. For these analyses, statistical significance was defined as $P<0.05$ (two-tailed).

3. Results

3.1. Comparison of volumes of regions of interest (ROI) between groups

Repeated measures ANCOVA revealed a significant main effect of diagnosis for the orbital gyrus ($F=7.18$, $df=1,71$, $p=0.009$), but not for the straight gyrus ($F=2.53$, $df=1, 71$, $p=0.116$). The post hoc test showed a significant cortical volume reduction of the bilateral orbital gyri in the schizophrenia patients ($p=0.022$ for the left hemisphere and $p<0.001$ for the right hemisphere, respectively). There was no significant difference in the ICV between the groups. Neither a significant main effect of gender/hemisphere nor an interaction among the factors was observed (Table 3).

3.2. Sulco-gyral pattern and volume of ROI

In schizophrenia patients, the OFC sulco-gyral pattern distribution of the right hemisphere was significantly different from that of the healthy subjects ($\chi^2=7.73$, $p=0.021$), while that of the left hemisphere did not differ between the groups ($\chi^2=0.24$, $p=0.89$). The alterations in the distribution of the right OFC sulco-gyral pattern in the schizophrenia patients was accounted for by decreased Type I expression and increased Type III expression among the patients compared with the healthy subjects (Table 4).

One-way ANCOVAs for volumes of the orbital gyrus and the straight gyrus with the OFC sulco-gyral pattern as a between-subject factor did not show any significant main effect or interaction.

3.3. OFC volume and clinical measures

For schizophrenia patients, the relative left orbital gyrus volume was significantly correlated with their SES scores ($r=0.360$, $p=0.019$), SES category (rho $=-0.393$, $p=0.010$) (Fig. 3), and illness duration (rho $=-0.347$, $p=0.024$) (Fig. 4). When we analyzed the education/occupation scores of SES

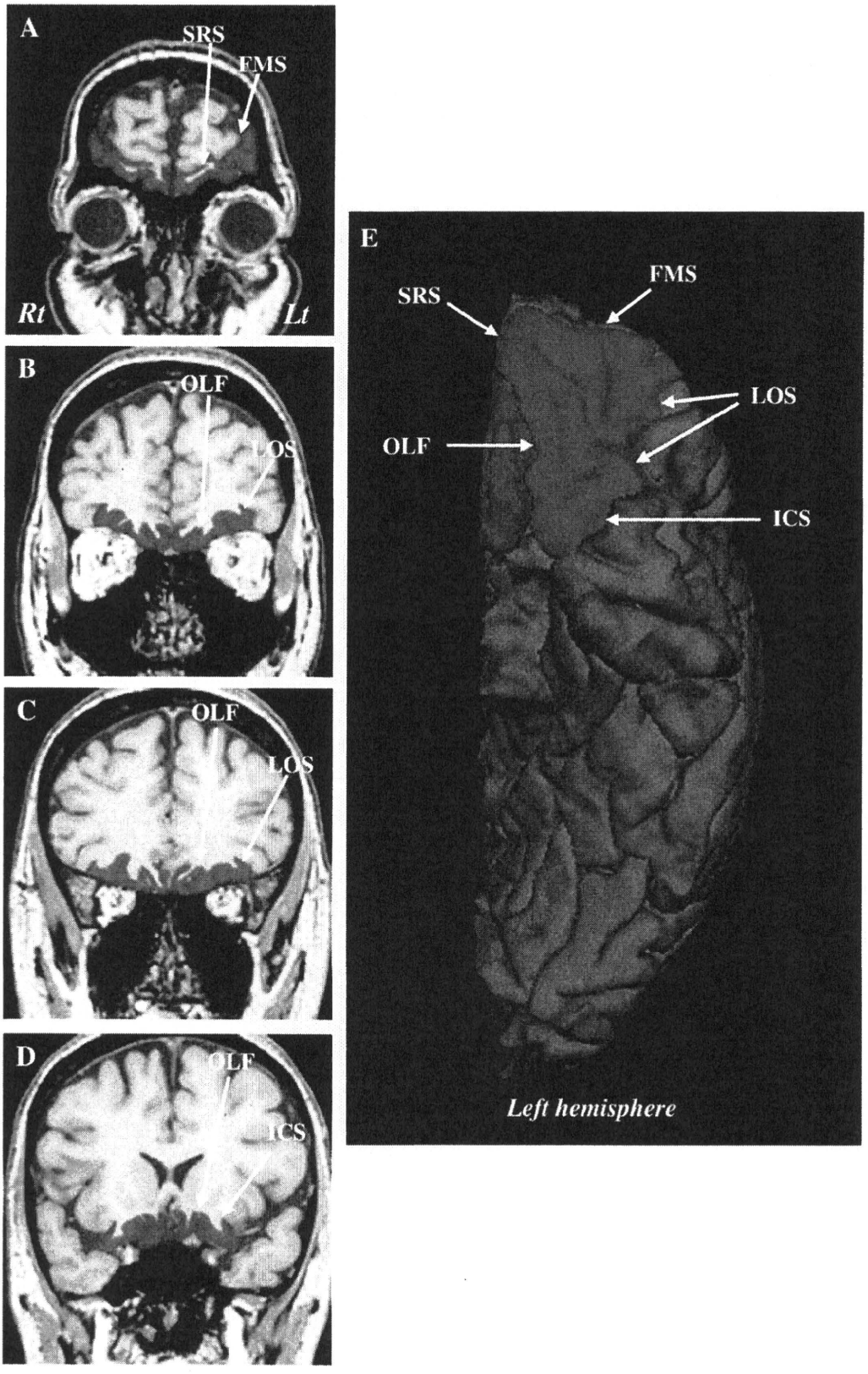

Fig. 1. Examples of regions of interest measured in this study on coronal view [(A) anterior part, (B) (C) intermediate part, and (D) posterior part] and ventral view (E). The OFC subregions are differentially colored in blue (orbital gyrus) and red (straight gyrus). Lt, left hemisphere; Rt, right hemisphere; FMS, frontomarginal sulcus; ICS, inferior circular sulcus; LOS, lateral orbital sulcus; OLF, olfactory sulcus; SRS, superior rostral sulcus.

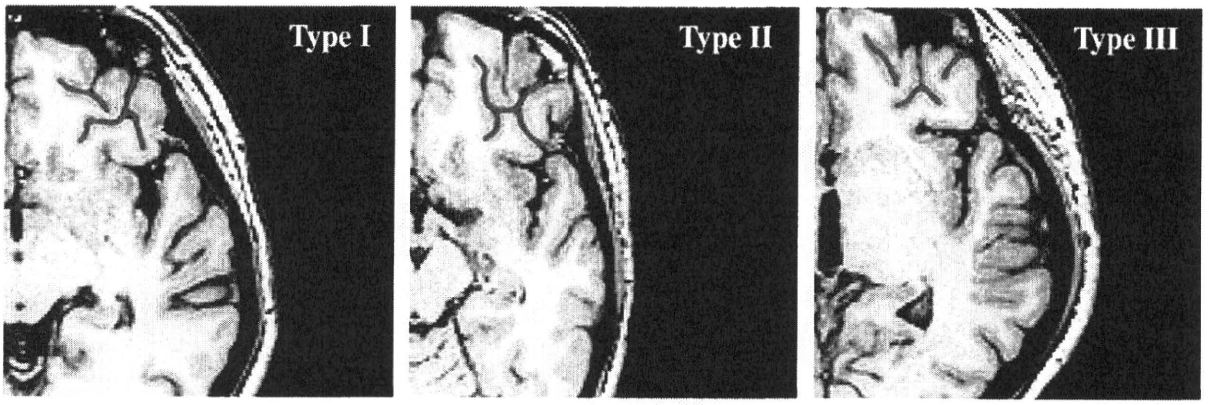

Fig. 2. Examples of the OFC sulco-gyral patterns (Types I, II, and III) from three left hemispheres on the axial view.

separately, both the education scores ($r = 0.325$, $p = 0.037$) and the occupation scores ($r = 0.305$, $p = 0.049$) were correlated with the left orbital gyrus volume. No significant correlation was found between ROI volumes and other clinical variables among patients (i.e., parental SES, duration of untreated psychosis, duration of medication, daily antipsychotic dosage, BPRS total and positive/negative scores).

In healthy subjects, no significant correlation was found between regional brain volumes and demographic measures including the SES.

3.4. Sulco-gyral pattern and clinical measures

In schizophrenia patients, ANOVA did not show any significant main effect of the OFC sulco-gyral pattern on any of the clinical measures used as a dependent variable (Table 5). Among the control subjects, a significant main effect of the OFC sulco-gyral pattern for parental SES was observed in the left hemisphere ($F = 3.59$, $p = 0.040$). However, a post hoc test did not show statistical significance ($p = 0.095$ for Type I versus Type II, $p = 0.095$ for Type I versus Type III, and $p = 0.944$ for Type II versus Type III, respectively) (Table 5).

4. Discussion

To the best of our knowledge, this is the first MRI study to report both the subregional volumes and sulco-gyral pattern of the OFC in first-episode schizophrenia. In this study, we demonstrated bilateral gray matter reduction of the orbital gyrus, but not of the straight gyrus, in patients with first-episode schizophrenia. These patients also exhibited altered OFC sulco-gyral patterns (decreased Type I and increased Type III expression) compared with the healthy controls in the right hemisphere. In addition, the smaller volume of the left orbital gyrus seen in the schizophrenia patients was related to lower SES and longer illness duration. Our findings implicate OFC morphologic changes, which are unlikely to be due to chronicity of the illness or medication effects, in the pathophysiology of schizophrenia.

4.1. OFC volume reduction in schizophrenia patients

Consistent with recent MRI studies (Kim et al., 2007; Nakamura et al., 2008; Venkatasubramanian et al., 2008; Schobel et al., 2009; Witthaus et al., 2009), we demonstrated that the cortical volumes of the bilateral orbital gyri were significantly reduced in schizophrenia patients compared with those in healthy subjects. The discrepancy between the results of this study and those of other ROI-based studies (Baaré et al., 1999; Crespo-Facorro et al., 2000; Yamasue et al., 2004; Shad et al., 2006; Lacerda et al., 2007; Sapara et al., 2007) can be partly explained by the different ROI definitions used. We measured the OFC subregions (i.e., the orbital gyrus and straight gyrus) on the basis of the optimized ROI definition used by Nakamura et al. (2008), who found similar

Table 3
Comparison of the ROI volumes.

Regions of interest	Schizophrenia patients ($n = 42$)	Control subjects ($n = 35$)	ANCOVA main effects					
			Diagnosis		Gender		Hemisphere	
			F	p	F	p	F	p
Intracranial volume	1492.1 ± 141.8	1533.9 ± 127.9	2.70	0.105				
Orbital gyrus								
Left	12.07 ± 2.01	13.25 ± 1.99	7.18	0.009*	0.04	0.841	0.15	0.699
Right	11.56 ± 1.63	12.91 ± 2.60						
Straight gyrus								
Left	3.05 ± 0.46	3.24 ± 0.42	2.53	0.116	0.07	0.789	1.81	0.183
Right	3.36 ± 0.56	3.64 ± 0.58						

Values represent mean ± SD of measured volume (cm^3). ANCOVA, analysis of covariance.
* For the results of the post-hoc tests, see the text.

Table 4
Distribution of OFC sulco-gyral pattern.

	Schizophrenia patients		Control subjects		Chi-square test	
	N	%	*N*	%	χ^2	*p*
Left hemisphere						
Sulco-gyral pattern						
Type I	20	48	18	51		
Type II	13	31	11	31	0.24	0.89
Type III	9	21	6	17		
Right hemisphere						
Sulco-gyral pattern						
Type I	13	31	20	57		
Type II	16	38	12	34	7.73	0.021
Type III	13	31	3	9		

OFC changes as in this study. Lacerda et al. (2007) demonstrated volume increase of the left OFC in first-episode schizophrenia, but their 'geometrical method' only assessed the anterior part of the OFC. Differences in sample characteristics (first-episode or chronic patients, gender ratio, severity of symptoms) might have also been related to the inconsistent OFC findings. The negative findings of several previous studies that mainly employed chronically treated patients (Baaré et al., 1999; Yamasue et al., 2004; Sapara et al., 2007) might have been partly due to the neuroprotective effect of antipsychotics (Lieberman et al., 2005; Molina et al., 2005; Van Haren et al., 2007). Several ROI-based studies examined only male patients (Baaré et al., 1999; Crespo-Facorro et al., 2000; Convit et al., 2001; Chemerinski et al., 2002; Nakamura et al., 2008), whereas one study demonstrated OFC volume reduction in female patients only (Gur et al., 2000). Since the severity of both positive (Nakamura et al., 2008) and negative (Baaré et al., 1999; Gur et al., 2000) symptoms as well as poor social functioning (Gur et al., 2000; Chemerinski et al., 2002; Koutsouleris et al., 2007) has been linked with smaller OFC

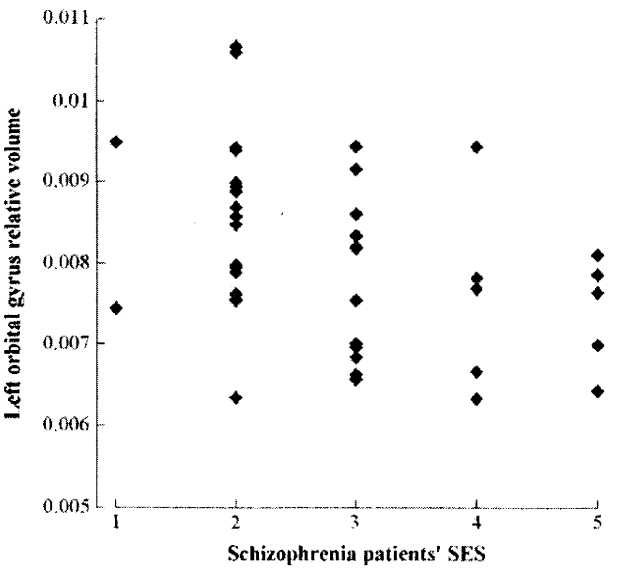

Fig. 3. Correlation between schizophrenia patients' SES and the relative volume of the left orbital gyrus. A smaller left orbital gyrus volume was negatively associated with the patients' SES (rho = −0.395, $p = 0.010$). Note that a smaller numerical value of SES indicates a higher social position.

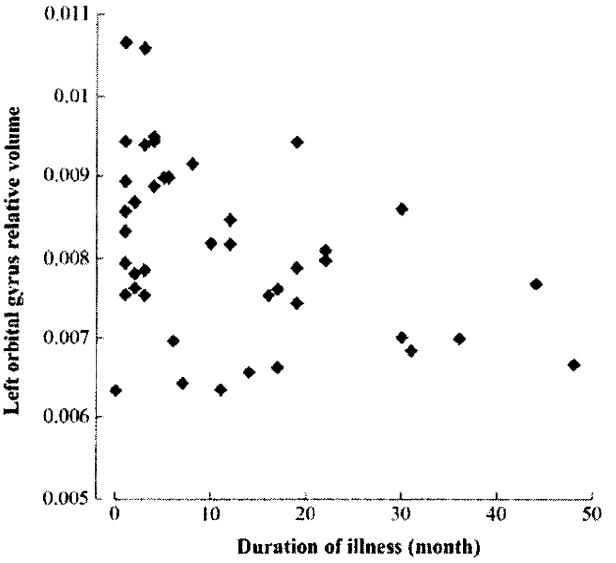

Fig. 4. Correlation between duration of illness and relative volume of the left orbital gyrus. There was a significant inverse correlation between the illness duration and the volume of the left orbital gyrus (rho = −0.347, $p = 0.024$).

volumes in schizophrenia, differences in these clinical factors might also be relevant to the discrepancies in OFC volumetric analysis results.

There is evidence for gender differences in brain structures among healthy subjects (Cosgrove et al., 2007) and gender-specific brain morphologic changes have been described in schizophrenia (Goldstein et al., 2002; Gur et al., 2000; Takahashi et al., 2002). Especially, Gur et al. (2000) demonstrated volume reduction of the OFC only in female patients. Although the present study showed no gender effects on the OFC volume in both schizophrenia patients and healthy controls, possible gender differences of the OFC morphology need to be further tested in a larger sample.

Our finding of a negative correlation between the volume of the left orbital gyrus and illness duration suggests the possibility of progressive volume reduction of the OFC during the early course of schizophrenia. Although no ROI-based MRI study has ever specifically examined OFC volume changes over time, recent longitudinal MRI studies demonstrated progressive volume reduction of the PFC in first-episode schizophrenia (Farrow et al., 2005; Nakamura et al., 2007b; Reig et al., 2009; Sun et al., 2008). Moreover, VBM studies in individuals at high risk of developing psychosis have demonstrated progressive OFC volume decrease during the transition to psychosis (Pantelis et al., 2003; Borgwardt et al., 2008). The present and these previous findings thus support the notion that dynamic brain changes occur during the earliest stages of schizophrenia (Pantelis et al., 2005).

4.2. OFC sulco-gyral pattern

In the present study, the distribution of OFC sulco-gyral patterns in the schizophrenia patients was significantly different from that of the healthy subjects. Consistent with a previous study (Nakamura et al., 2007a), alterations in the OFC sulco-gyral pattern distribution due to deceased Type I expression and increased Type III expression in schizophrenia

Table 5
Clinical parameters and sulco-gyral pattern.

Clinical measures	Hemisphere	ANOVA main effect of sulco-gyral pattern (Types I–III)			
		Schizophrenia patients		Control subjects	
		F	*p*	*F*	*p*
Subjects' SES	Left	0.61	0.212	3.23	0.053
	Right	0.59	0.558	0.00	0.995
Parental SES	Left	1.46	0.246	3.59	0.040[a]
	Right	1.42	0.254	0.38	0.69
Estimated IQ	Left	1.32	0.279	0.01	0.931
	Right	1.08	0.350	0.85	0.435
Duration of untreated psychosis	Left	0.11	0.900		
	Right	0.18	0.834		
Duration of illness	Left	0.04	0.965		
	Right	0.25	0.781		
BPRS total score	Left	0.52	0.600		
	Right	0.71	0.500		
BPRS positive score	Left	0.13	0.875		
	Right	1.42	0.254		
BPRS negative score	Left	1.58	0.218		
	Right	0.68	0.514		

ANOVA, Analysis of variance; BPRS, Brief Psychiatric Rating Scale; SES, Socio-economic status.
[a] For the results of the post-hoc tests, see the text.

patients was limited to the right hemisphere. Moreover, in our sample, the alteration of the OFC sulco-gyral pattern distribution in patients was independent of the OFC volume changes. Since sulcal/gyral folding is almost completed by the third trimester of gestation (Chi et al., 1977; Worthen et al., 1986) and structural stability of the folding is generally achieved from soon after birth (Armstrong et al., 1995), the altered sulco-gyral pattern of the OFC seen in the patient group may reflect a neurodevelopmental abnormality in schizophrenia.

Gross brain abnormalities in schizophrenia have already been reported, including the lack of normal leftward sulcal asymmetry of the anterior cingulate cortex (Yücel et al., 2002; Le Provost et al., 2003; Fujiwara et al., 2007). Abnormal asymmetry of prefrontal gyral complexity in schizophrenia has also been demonstrated by both postmortem (Vogeley et al., 2000) and MRI studies (Vogeley et al., 2001; Wiegand et al., 2005). The altered OFC sulco-gyral pattern confined to the right hemisphere in the patient group may have been caused by a neurodevelopmental abnormality occurring in the earliest period of life. Genetic aberrations and/or their interactions with the environment may have contributed to these hemisphere specific-changes, since several sets of genes have been identified as candidates for the evolution of human hemispheric asymmetry (Sun et al., 2005; Sun et al., 2006), which is present as early as 20–22 weeks gestational age (Hering-Hanit et al., 2001).

Nakamura et al. (2007a) examined the OFC sulco-gyral pattern of established schizophrenia patients (duration of illness median = 19.5 years) and found relationships between Type III expression, which was increased among patients, and lower SES, poorer cognitive function, and more severe symptoms, whereas Type I expression was implicated in better cognitive function and milder symptoms. However, we did not find any relationship between the OFC sulco-gyral pattern and clinical variables in first-episode patients. These findings suggest that the altered sulco-gyral pattern could affect the later clinical course of schizophrenia, as demonstrated in chronic patients (Nakamura et al., 2007a), rather than the clinical features of the early phase of illness.

4.3. OFC volume and socio-economic status in schizophrenia patients

In this study, the SES of the first-episode schizophrenia patients was significantly related to the left orbital gyrus volume reduction. Lower social functioning and social status have been repeatedly described in schizophrenia patients (Goldberg and Morrison, 1963; Cohen, 1993; Agerbo et al., 2004). The social dysfunction of schizophrenia patients is probably due to multiple factors such as neurocognitive deficits, lower childhood socio-economic status, and positive and negative symptoms (Wicks et al., 2005; Mohamed et al., 2008). Given the functional significance of the OFC in various cognitive and emotional functions (Hornak et al., 2003; Kringelbach, 2005; Rolls and Grabenhorst, 2008), it can be speculated that the OFC volume deficit gives rise to impaired decision making, lack of affects, inappropriate behavior, and irresponsibility, all of which could affect their social functioning.

Epidemiologic studies have shown that such social impairments are already seen in individuals in the prodromal phase (Häfner et al., 1995; Yung et al., 2003; Mason et al., 2004; Addington et al., 2008). Although the current study cannot address the question of whether the OFC volume reduction occurs and affects subjects' social functioning during the prodromal phase of schizophrenia, the relationship between smaller OFC volume and worse premorbid social functioning in chronic schizophrenia patients (Gur et al., 2000; Chemerinski et al., 2002) and the progressive OFC volume decrease during the transition to psychosis demonstrated previously (Pantelis et al., 2003; Borgwardt et al., 2008) suggest that the structural changes in the OFC and social dysfunction may have developed before/during the onset of overt psychosis.

4.4. Limitations

A few potential confounding factors in this study should be taken into account. First, this study was partly limited by a lack of a comprehensive assessment of neuropsychological functioning (e.g., decision making ability), as previous MRI studies demonstrated the relationship between OFC morphology and cognitive functioning in both schizophrenia patients and healthy control subjects (Nakamura et al., 2007a, 2008). Second, other brain regions that might be associated with social functioning were not measured in the current study. For example, several studies have suggested relationships between social impairment and structural changes in brain regions including the DLPFC (Prasad et al., 2005), anterior cingulate cortex (Fujiwara et al., 2008), and fusiform gyrus (Onitsuka et al., 2005) in patients with schizophrenia. Third, although we examined the patients during their first-episode, all patients had received antipsychotics prior to scanning, even if only for a short period. As there is evidence for antipsychotic medication affecting brain morphology (Lieberman et al., 2005; Molina et al., 2005; Van Haren et al., 2007), future research should examine drug-naïve

patients to fully exclude the influence of antipsychotic medication. Fourth, the patient group in this study was relatively old for first-episode psychosis group (approximately 29 years old), raising the possibility that our sample might not be representative of the general population. Thus, potential sampling bias may limit the ability to generalize the findings from the present study. Finally, since abnormalities of the OFC are likely to be involved in the pathophysiology of other psychiatric disorders (e.g., bipolar disorder; Stanfield et al., 2009), the disease specificity of our findings needs to be tested in future studies.

5. Conclusion

We demonstrated both gray matter reduction, which was localized to the orbital gyrus, and an altered sulco-gyral pattern of the OFC in patients with first-episode schizophrenia. These OFC structural abnormalities might reflect both neurodevelopmental (sulco-gyral pattern) and neurodegenerative (gray matter reduction) changes in schizophrenia patients. Our findings also suggested a relationship between the OFC volume deficits and social functioning impairment in schizophrenia patients even at their first hospitalization.

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Contributors

Authors YT and MS designed the study and wrote the protocol. Authors YT, LO, YM and YS did MRI/clinical data gathering. Authors YT and NM performed MRI data analyses. Author YT wrote the first draft of the manuscript. Authors MS, TT, YK and KN supervised the brain volumetric analyses and the statistical analyses. Authors MS, TT, YK, KN, MI, HY, KK and YO supervised the overall research project and revised the manuscript. Authors MS and TT contributed to editing the final manuscript. All authors have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflict of interest.

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