るかどうかを十分に確認し，双方の主観に配慮しながら，対話の中で治療の短期目標と長期目標を明確にしていく。

SDMでは，その場で治療方針が決定できなければ決定を延期することもできるとされており，緊急時の対応には適さない。しかし治療者と患児，家族が話し合いの場を持つことにより，患児は自分が尊重されている感覚や，自分自身で問題に対処しているという自己効力感を持って治療を受けることができ，より主体性を持った治療参加につながるものと期待される。

V．SDMの実際

以下に示す症例は，注意欠如多動性障害の診断により医学的には薬物療法の開始が適切であると考えられたが，両親が薬物療法に抵抗を示していた例である。この症例を通じて，SDMのプロセスを見ていくこととする。なお症例は，個人が特定できないよう背景情報および経過の詳細に改変を加えている。

症例：小学校4年生の10歳男児。担任教師の勧めにより，両親とともに発達障害クリニックを受診した。

幼少児より言語運動発達の遅れ，奇抜なこだわりは認められなかったが，落ち着きはなく，運動会，学芸会等の行進や体操等の集団行動でも一歩遅れ，幼稚園の教師より注意を受けることが多かった。小学校入学後，当初授業中の立ち歩きが目立ったが，教師から注意を受けることで，一時的ではあるが態度は改善した。また，頻回に忘れ物をするため翌日の学校の準備は必ず母親と一緒に行っていた。次第に机の上での手わるさが増え，それに飽きると居眠りをするようになった。家で終わらせた宿題も翌日に提出し忘れ，翌日に必要な物等の担任教師からの連絡事項も記録することができず，授業内容の理解の不良も目立ってきた。家庭では，学校の宿題，自主学習に取り組む時間は専業主婦の母親が付き添って行う30～60分程の時間のみで，食事，入浴等生活に必要な時間以外は，テレビを見たり，テレビゲームをしたりして過ごした。小学校4年生の時点で，担任教師より児童精神科医師への相談を勧められ，両親とともに発達障害クリニックの児童精神科を受診した。

担当医師は，上記の担任教師の手紙からの情報，両親からの家庭の様子の話より，注意欠如多動性障害，知的障害を疑い，知能検査を施行した。知能検査の上では，知的な遅れは認めなかったが，聴覚的短期記憶能力の苦手さを認めたことも合わせ，注意欠如多動性障害と診断した。まず家庭と学校の環境調整，両親に対して，両親自身へのペアレントトレーニング，本人に対するトークンエコノミー等の行動療法的なアプローチを勧めた。その後，月2回1回1時間のペアレントトレーニングに母親が参加し，行動療法的なアプローチも半年間程続けたが，本人の症状は著明には改善せず，忘れ物の多さからクラスメートよりいじめを受けていることもあったため，担当医師は薬物療法が必要と判断した。

担当医師は薬物療法を受けることの利益とともに，短期的には食欲低下，体重減少，頭痛，不眠等，長期的には成長が抑制される可能性があること等の副作用を中心に薬物療法を受けることの不利益，学習が遅れる，いじめが助長され不登校となる可能性等薬物療法を受けないことの不利益を両親と本人に図を用いて説明を行った。本人は説明を十分に理解できたようであり，多少薬の副作用があっても困っていることが良くなるなら薬を飲んでみてもよいとのことであった。しかし両親は薬物療法への不安が強く，再びペアレントトレーニングのみの治療を希望した。

医師は，行動療法，ペアレントトレーニングを継続するのみでは，本人の症状の改善も限定した効果に留まる可能性があることを説明し，自宅でもう一度話し合ってみるよう促したが，両親の意見は変わらなかった。両親は，インターネットその他から薬害についての多くの情報を得ており，可能であれば薬物療法以外の治療で状況を改善していきたいと強く希望していた。しかしそれから3ヵ月が経過した後も状況は改善せず，いよいよ授業内容の理解が困難になり，さらに授業中居眠りする時間が増え，成績も徐々に下がった。この

時点で再度両親と本人に薬物療法のリスクとベネフィットにつき説明を行い，本人および両親が十分納得したうえで薬物療法が開始となった。

この症例では，本人は薬物療法を希望しているが，両親の薬物療法に対する不安が強く，双方の価値観にずれが生じている。児童思春期精神医学の領域においては，本人と家族の意向が異なり，治療者がどちらの意向を重視するべきかで対応に苦慮する場面に遭遇することも少なくない。SDMモデルにおいては，治療者が家族内での対話も促進できるよう関わりながら，このずれを徐々に修正していく。このため緊急性が高くない場合には，治療者が医学的に有効であると考える治療を差し控えざるを得ない状況も生じ得る。

しかしながら特に薬物療法を開始する際には，児童思春期に対する有効性と安全性が十分確立していないことや，治療が長期にわたる場合も多いこと，家族関係が病状に与える影響も大きいことなどを考慮すると，時間をかけて本人および家族の主体的な治療参加を促していくことの治療的意義は大きい。このような対応を精神科医のみで行うことは時間的な制約などから困難であり，多職種チームによる対応が求められる。

Ⅵ．おわりに

児童思春期精神医学領域においては，「精神疾患を持つ子ども」という極めて脆弱な立場にある個人とその家族に対応しなくてはならない。子どもに対する薬物療法の有効性と安全性が確立されているとは言い難い状況の中，インターネットや各種メディアにあふれる玉石混交の情報から，必要以上に治療に不安あるいは期待を抱く本人や家族も少なくない。

このような状況において患児にとって最善の利益となる治療を提供するためには，治療方針決定の際に治療者と本人，治療者と家族，そして家族間における双方向性の対話が必要である。患児や家族が主体的に治療に取り組めるような治療同盟の構築は，治療の成否の鍵ともなり得ることを我々は十分に認識する必要があるとともに，そのような対応が可能な精神保健医療のシステムの構築が求められる。

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特集　早期介入の実際と工夫

デイケア施設を活用した包括的早期介入の試み：イルボスコ

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近年，精神病未治療期間（DUP）の短縮，治療臨界期内の集中的治療が予後決定因子として注目を集め，統合失調症の早期介入として，世界各国で様々な援助サービスや治療法が提案されている．東邦大学医療センター大森病院では，顕在発症予防の視点に立った前駆期の介入として，通所型早期精神病ユニット「イルボスコ」を立ち上げ，脳機能への直接的介入を目指した認知機能訓練，思春期・青年期に配慮した認知行動療法的アプローチを両軸とする心理社会的治療を基としたプログラムを用いて早期介入を実現している．本稿では，「イルボスコ」で用いられる具体的なアプローチ法について概説し，今後の課題について考察した．

＜索引用語：早期介入，精神病未治療期間，治療臨界期，精神病発症危険状態，早期介入ユニット＞

はじめに

統合失調症の早期介入に関しては，精神病症状出現から精神科治療が開始されるまでの期間である精神病未治療期間（duration of untreated psychosis：DUP）の短縮，発症後2～5年以内の期間といわれる治療臨界期（critical period）内の集中的治療の重要性が広く認識されている．その効果は，社会機能の低下や再発リスクの低減，入院必要性の減少などを通じて予後を良くすることとして諸外国を中心に現在までに数多く報告されている[6]．統合失調症をはじめとする精神疾患が思春期・青年期前期に好発することが知られており，この時期が成長・教育の過程にある重要な時期に相当する．このため，罹患者が社会から分断されないように，そしてより健康な成長・教育を支援するという意味で，より早期に適切な介入を行う必要性があると考えられている．世界各国で積極的な働きかけ，包括的な支援などの取り組みが行われているが，国内ではまだそのような取り組みが行われつつあるものの不十分な状態にとどまっているのが現状である．

Ⅰ．通所型早期精神病ユニット（イルボスコ）の取り組み

1．施設概要

上述のような潮流の中，東邦大学医療センター大森病院では，早期精神病ユニット（Early Psychosis Unit：EPU）を2007年5月に大規模認可のデイケアとして開設し，「イルボスコ」と命名した．目的は，統合失調症の前駆状態から顕在発症への進展を頓挫させる介入，発症間もない初回エピソード統合失調症の方々に対して，社会復帰を目標とする積極的なリハビリテーションである．対象は15～30歳の精神病発症危険状態（At Risk Mental State：ARMS）や初回エピソード統合失調症（first episode schizophrenia：FES）などの早期精神病者（early psychosis）とし，発達障害は除外している．スタッフは2012年2月現在，看護師，作業療法士，臨床心理士各1名の計3名の常勤者と，それに加え，担当医（精神科医）2名，

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	月	火	水	木	金
午前	認知機能 ゲーム	料理	アニメーション 学院	書道/英会話/ PC/合唱	コミュニケーション グループ
午後	ヨガ	創作	スポーツ	みんなの時間 ＋ リラクセーション	心理教育/ 勉強会
終了後	就労グループ	部活	話し合い	ボスコゼミ/運動	部活/総会
	認知機能 ワークシート	認知機能 ワークシート	認知機能 ワークシート	認知機能 ワークシート	認知機能 ワークシート

図1　イルボスコ1週間のプログラム例

臨床心理士1名の兼任者，前期研修医が1日1名参加し，その他プログラムのボランティア講師や非常勤協力者が適宜参加している．大学病院であり，人員，職種が豊富なことなどのメリットを活用し，1日平均6〜7名の治療スタッフが参加している．インテンシブなリハビリテーションを目的とするため，利用期限を1年間としている．

イルボスコ利用導入に至るまでの受診経路として，ウェブサイトやパンフレットの情報を参考に来られる方，学校の先生からの勧めで来られる方，地域の開業医の先生からの紹介で来られる方がいる．当院外来の受診に至った方には，PRIME-Jスクリーニング[3]，Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms（SIPS/SOPS）[4]，各種心理検査などを用いた診断，アセスメントを行っている．その中でARMS，FESが疑われた症例に対して速やかに2名のイルボスコ担当医いずれかの診察が行われ，導入を判定される．受診経路について調査を行ったところ，比較的遠方からの参加者もみられる中，施設近隣在住者に多い傾向，交通アクセスが良好な鉄道沿線に多い傾向が認められている．

イルボスコで行っているプログラムは，認知機能トレーニングと，認知行動療法的アプローチを両軸とした心理社会的アプローチを基として組み立てられている．ポイントはツールやゲームを用いた認知機能トレーニング，ロールプレイやシートを用いた対人関係技能の習得および向上，本人の疾病管理や生活支援などを念頭においた心理教育，そして成長過程で経験し得なかった集団体験を目的としたグループワークを部活動や文化祭などを通じて行っていることである．対象者の多くが，思春期・青年期前期に相当する時期であることを踏まえプログラムを作成し，適宜見直しを行っている．実際に行っている1週間のプログラム例を示す（図1）．プログラムは固定ではなく，その時のメンバーの状態を含めたニーズに対応して随時変更を加えている．プログラム開始前の時間を用いて部活動の朝練を行ったり，プログラム終了後に個別の面談も行っている．

2．認知機能トレーニング

統合失調症での認知機能障害は，陽性症状や薬物療法との関係性は薄く，陰性症状との関連性も若干であることが知られる一方で，社会機能障害との関連が深く，生活のしづらさや，予後に深く関わると考えられている[2,7]．認知機能ゲームやワークシートは，記憶機能や注意機能など要素的認知に着目している．「聖徳太子ゲーム」は，各々異なる物語を読む2人の話者の内容を中央の1人が聞き取り，いずれか一方の内容を聞き取るという注意・集中力を要する課題となっている．認知機能障害のうち，特に発散的思考（divergent thinking）の障害は，社会機能障害との深い関連性が指摘され[8]，発散的思考の障害を標的とした集中的な認知機能訓練の効果がすでに実証されている[9]．イルボスコにおいても同訓練を実施している（図2）．

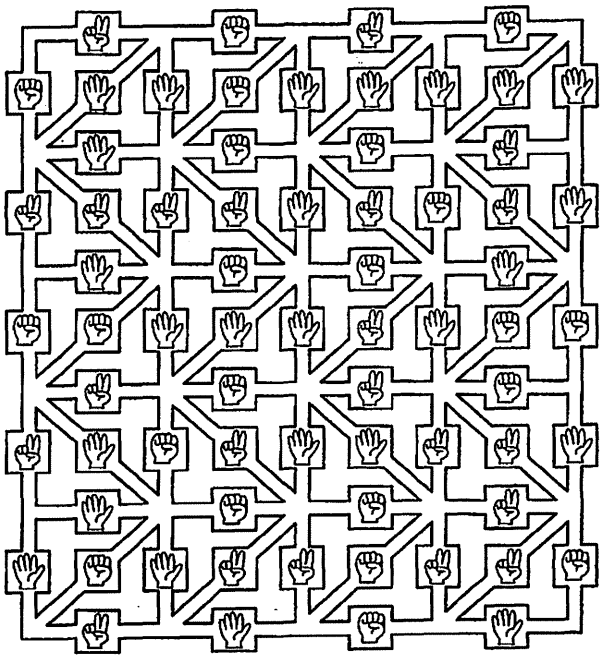

図2 発散的思考を標的とした認知機能訓練課題の1例

その他のプログラムも認知機能に働きかけるように作成されている．創作プログラムは，注意機能，作業速度など要素的認知機能を意識して作成されており，アロマオイル作り，絵本，セル画制作などを行っている．料理プログラムは調理過程における認知機能に留意し，メニュー決め，材料購入，調理，盛り付け，実食の各作業段階で，計画力，流暢性，注意機能，巧緻機能，コミュニケーション能力などに留意した働きかけを行っている．英語プログラムは，専任講師により行われ，コミュニケーション技能への働きかけを重視している．スポーツプログラムでは，注意機能，運動速度，協調運動への働きかけに着目するとともに，ストレスコーピングの一法として，バスケットボール，フットサル，バドミントンなどを行っている．

3. OTPに則った認知行動療法的アプローチ

認知行動療法的アプローチとして，Falloon, I. R. H. による統合型地域精神科治療プログラム（Optimal Treatment Project：OTP）に則りプログラムを作成している[1,5]．これは，当事者の生活

図3 リハビリテーションワークブック

場面の中で認知行動療法的介入や環境調整を行うことにより，当事者とその家族に対してエンパワメントを行う手法であり，イルボスコでもプログラム開発の他，スタッフの全般的な関わり方のモデルとしている．具体的には，①ロールプレイやシートを用いた対人関係技能の習得および向上，②疾病管理と生活支援，③集団体験を目的としたグループワークである．ロールプレイやシートを用いた対人関係技能の習得および向上の一環として，精神科リハビリテーションワークブック（図3）を用いた疾病教育，オリジナルのワークシートを用いた問題解決技法の学習，実際に患者家族に起こるであろう場面を想定したシナリオに沿ったロールプレイを行っている．疾病管理と生活支援の一環として，包括的医療を念頭においた利用者や家族への心理教育プログラムを行っている．利用者の方々に対して，医師，作業療法士，看護師，薬剤師，臨床心理士など多職種で連携し，疾病，薬物療法，ストレス対処法などを説明している．そして，理解力，知識の般化に個人差が生じる可能性も考慮しオリジナルシートなどを用いた般化の工夫，個別的フォローを行っている．家族に対しても，当事者が多様な病期あるいは病状にあり，家族もそれを踏まえた上での対応が必要であ

ること，家族自身も混乱していることも少なくないことを考慮し，月に1回の頻度で家族心理教育を行っている．集団心理教育を中心にストレスマネージメントの指導を行い，個別の支援的介入により家族自身の行っているコーピング戦略について必要に応じて介入している．

4．思春期心性へ配慮した取り組み

学校生活であれば体験するであろう集団生活が体験できない状況にあるために，集団生活での対人関係に自信を喪失している例もみられる．集団体験を目的としたグループワークの一環として，料理プログラム，英語プログラム，部活動や文化祭，フリーマーケットへの参加，外出プログラムを行っている．思春期・青年期前期は一般的に年齢，就労ステータスに関して同質な集団で過ごす時期が多く，利用者の中には同世代の若者と比較し，焦りや挫折感をもつことも多いため，その気持ちに配慮しながら，自らが社会に対して何らかの役割を果たしているという自己効力感や自信，また，コミュニケーション技能の獲得に主眼をおいて進めている．疾病からの回復のみでは彼らの自己効力感の回復を含めた全人的な回復概念を達成することは困難と考え，学校や企業などとも連携し包括的なケースマネージメントを行えるよう日々工夫を重ねている．学園祭や体育祭，勉強時間，部活など集団生活体験の機会を可能な限り提供し，場合によってはセンター試験の模擬試験なども行っている．

5．イルボスコ開設5年目を迎えた取り組みの成果

これまで，イルボスコでの試みを通じてサイコーシス早期段階の就労・就学支援の重要性を報告し，登録期間1年以内に本人が希望する形での社会参加が可能となった割合をre-start rate（RR）と定義し，イルボスコの利用が一定の社会参加を促していること，本人の興味や好みをプログラム内で同定し，それに基づいた職場探しを行うindividual placement and support（IPS）に準じた支援が自己評価の改善やレジリエンスの強化につながることなどを報告してきた[10]．開設約5年の活動成果としては，登録期間終了者，卒業者合わせて75名，イルボスコ登録期間中に本人が希望する形での社会参加が可能となった登録者45名であり，登録1年以内で60.0%の利用者が本人の希望する形での社会参加が可能であった．この社会参加の就労は障害雇用ではなく主に一般就労である．また，今回はイルボスコ利用からの治療脱落率を算出した．海外の報告では，抗精神病薬投与群のみの薬物療法単独群，薬物療法に12ヵ月間の心理社会的治療を追加した併用群とで治療脱落率を比較した1年間の無作為化比較試験の報告があり，その中で心理社会的治療併用群の治療脱落率は，薬物療法単独群よりも良好な結果であった．イルボスコ利用者の中で，イルボスコ登録期間中に3ヵ月以上利用途絶し，かつ社会的転帰が不良の方の比率を治療脱落率（drop-out rate：DR）として定義し，算出した結果11.9%と海外の報告と比べても低値であった．

Ⅱ．今後の課題・展望

開設5年目を迎え，イルボスコの現状と今後の課題・展望について以下の3点より考察した．

まず1点目は，社会復帰の推進である．上述の通り，イルボスコでの社会復帰率は比較的良好と考えられたが，この理由として，プログラムと並行して面接などの個別対応を行い，登録者に対してインテンシブな介入を行っているためと考えられた．従来型のデイケアに加え，より人的資源を要する急性期に特化したデイケアが付加的に必要であり，より就学・就労に特化したプログラム内容を検討していく必要性を示していると考えられた．

2点目は，利用脱落率の低減である．上述の通り，利用脱落率は海外の報告と比べても低値であった．従来型のデイケアと比較すると平均年齢も若いことを想定し，思春期特性を踏まえたプログラムを作成していることが理由として挙げられる．対象がある程度均一であることも踏まえ，そ

のような背景要因にあわせたプログラムの開発と発展，モチベーションへ働きかける対応が今後も必要と考えられた．

3点目は，利用者数の増加である．開設後約5年間での総登録者数が113名と年間約20人程の登録にとどまった．施設の存在自体の普及・啓発が進んでいない可能性も考えられたが，主な利用者が施設近隣在住者に多い傾向がみられることから，今後交通アクセスを考慮した普及活動の必要性，イルボスコ同様の早期精神病ユニットの普及の必要性も考えられた．

おわりに

上述の3点より，早期精神病ユニットとして慢性期精神病ユニットとの機能分化を図ることが必要であり，今後の利用者数の増加に耐えうるスタッフ数の増加，施設数の増加を踏まえ，保険点数等の診療報酬上の優遇，差別化も踏まえて急性期精神病ユニットの重要性を検討していく必要性があると考えられる．

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Efforts toward Comprehensive Early Intervention at Early Psychosis Unit "Il Bosco"

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Recently, shortening of the duration of untreated psychosis (DUP) and intensive treatment within the critical period are taken as determinants of a favorable prognosis, and various service systems and treatment approaches for early intervention in schizophrenia have been proposed in the world. At the Toho University Omori Medical Center, Early Psychosis Unit "Il Bosco" was established as an intervention service from the viewpoint of preventing full-blown psychosis at the prodromal stage, where cognitive training for a direct therapeutic approach to brain function and psychosocial treatment for patients at puberty and adolescence are administered. In this article, we introduce the practice at "Il Bosco" and consider future prospects.

<Authors' abstract>

<**Key words**：early intervention, duration of untreated psychosis, critical period, at risk mental state, early psychosis unit>

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Altered depth of the olfactory sulcus in first-episode schizophrenia

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ABSTRACT

A shallow olfactory sulcus has been reported in chronic schizophrenia, possibly reflecting abnormal forebrain development during early gestation. However, it remains unclear whether this abnormality exists at the early illness stage and/or develops progressively over the course of the illness. This magnetic resonance imaging (MRI) study investigated the length and depth of the olfactory sulcus in 64 first-episode schizophrenia patients and 64 controls, of whom longitudinal MRI data (mean inter-scan interval = 2.6 years) were available for 20 patients and 21 controls. In the cross-sectional comparison at the baseline, the schizophrenia patients had a significantly shallower olfactory sulcus compared with the controls bilaterally, but there was no group difference in its anterior–posterior length. A longitudinal comparison demonstrated that the sulcus length and depth did not change over time in either group. The olfactory sulcus measures of the patients did not significantly correlate with clinical variables such as onset age, medication or symptom severity. These findings suggest that the olfactory sulcus depth, but not length, may be a static vulnerability marker of schizophrenia that reflects early neurodevelopmental abnormality.

1. Introduction

The depth of the olfactory sulcus, which appears in the fetal forebrain at around 16 weeks gestation (Chi et al., 1977), relates to olfactory function in healthy subjects and is usually deeper on the right hemisphere in association with functional lateralization in the olfactory system (Hummel et al., 2003). It is known that patients with congenital anosmia have a shallow olfactory sulcus, probably reflecting abnormal development of the olfactory system (Abolmaali et al., 2002; Huart et al., 2011). Given the evidence that schizophrenia patients exhibit olfactory dysfunction as a possible vulnerability marker (Brewer et al., 2001, 2003; Kamath et al., in press; Turetsky et al., 2009b), as well as the fetal stage of the sulcus formation at which neurodevelopmental disruption could increase the risk for schizophrenia (Fatemi and Folsom, 2009), the olfactory sulcus morphology in schizophrenia as a potential early neurodevelopmental marker is worth investigating.

To our knowledge, only two magnetic resonance imaging (MRI) studies have examined the olfactory sulcus depth in schizophrenia; Turetsky et al. (2009a) demonstrated an abnormally shallow olfactory sulcus in chronic patients of both genders, especially on the right hemisphere, whereas Nguyen et al. (2011) found a normal sulcus depth in male chronic patients. This inconsistency may be partly explained by different sample characteristics, as well as technical issues, as Nguyen et al. (2011) measured the sulcus depth using a single slice based on external landmarks [i.e., the plane of the posterior tangent through the eyeballs (PPTE)]. The results of Turetsky et al. (2009a) were based on the measurement of the entire structure, but their findings need replication, ideally in first-episode patients in a longitudinal design, in order to clarify the nature of olfactory sulcus abnormalities in schizophrenia.

This cross-sectional and longitudinal MRI study investigated the length and average depth of the olfactory sulcus in first-episode schizophrenia compared with healthy controls. On the basis of previous findings in chronic patients (Turetsky et al., 2009a) and the potential role of the sulcus depth as a neurodevelopmental marker, we predicted that patients would have a shallower olfactory sulcus compared with the controls at the baseline, and that the sulcus morphology would not change over time in either group. We also explored the relationship between the sulcus morphology and several clinical factors (e.g., symptom severity, antipsychotic medication) in schizophrenia.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CSP, cavum septi pellucidi; ICV, intracranial volume; MRI, magnetic resonance imaging; PPTE, plane of the posterior tangent through the eyeballs; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

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2. Methods

2.1. Participants

Sixty-four first-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003; Schooler et al., 2005; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=48$) or those undergoing their first psychiatric hospitalization ($N=16$). The diagnosis of schizophrenia was confirmed for all patients at least 6 months after the illness onset based on information obtained from a detailed chart review. Their clinical symptoms were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS; Andreasen, 1984). Medication and other clinical data are summarized in Table 1. Four patients were also receiving mood stabilizers [lithium carbonate ($N=1$), sodium valproate ($N=1$), or carbamazepine ($N=2$)] at the time of baseline scanning.

The control subjects consisted of 64 healthy volunteers recruited from the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g., history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (2 items) histories of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives.

All subjects were right-handed and physically healthy, and none of the participants were pregnant or taking exogenous estrogens at the time of the study. None had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. All participants were also screened for gross brain abnormalities by neuroradiologists. Follow-up MRI data were available for 20 patients and 21 controls; the characteristics of this sub-sample were largely comparable with those of the whole sample of this study (Table 1). The controls had attained a higher level of education than the patients, but the groups were matched for age, gender, height, parental education, and inter-scan interval (Table 1).

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

2.2. MRI procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time = 24 ms; echo time = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The follow-up data were acquired using the same scanner/parameters as described above. The scanner was calibrated weekly with the same phantom to ensure measurement stability. The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003); there was no group difference in the ICV (Table 1).

2.3. Olfactory sulcus measurements

For the assessment of the olfactory sulcus, the images were processed on a Linux PC (Fujitsu Limited, Tokyo, Japan) using Dr. View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure–posterior commissure line. One rater (TT), who was blind to the subjects' identity and time of scan, measured the depth of the olfactory sulcus, which could be readily identified in the coronal view, in all 1-mm coronal slices where the sulcus was clearly seen (Fig. 1). On each coronal slice, the olfactory sulcus was traced beginning with the deepest point of the sulcus and ending inferiorly with a tangent line connecting the top surfaces of the gyrus rectus and medial orbital gyrus (Rombaux et al., 2009). While previous

Table 1
Sample characteristics of the participants.

	Cross-sectional analysis			Longitudinal analysis		
	Controls	Schizophrenia	p	Controls	Schizophrenia	p
Male/Female	37/27	37/27	1.000	13/8	14/6	0.585
Age (years)	25.1 (5.0)	24.0 (4.7)	0.203	24.5 (5.0)	23.8 (5.0)	0.664
Height (cm)	167.0 (7.5)	164.9 (7.6)	0.109	167.3 (7.6)	166.2 (6.6)	0.606
Education (years)	16.5 (2.6)	13.5 (1.9)	<0.001	15.6 (2.4)	13.0 (1.6)	<0.001
Parental education (years)[a]	13.2 (2.5)	13.0 (2.0)	0.482	12.8 (2.6)	12.5 (2.1)	0.756
Inter-scan interval (years)	–	–		2.5 (0.4)	2.7 (0.8)	0.261
Onset age (years)	–	23.1 (4.7)	–	–	22.7 (5.1)	–
Illness duration at baseline (months)	–	11.2 (12.2)	–	–	10.2 (9.4)	–
Medication type (typical/atypical/mixed)						
At baseline	–	18/43/1[b]	–	–	6/12/2	–
During follow-up	–	–	–	–	3/13/4	–
Medication dose (haloperidol equivalent)[c]						
At baseline (mg/day)	–	10.3 (8.8)	–	–	14.6 (11.7)	–
Cumurative dose during follow-up (mg)	–	–	–	–	9852 (8727)	–
Duration of medication at baseline (months)	–	8.3 (12.6)	–	–	8.3 (10.1)	–
SAPS total at baseline[a]	–	27.3 (21.9)	–	–	33.0 (24.0)	–
SAPS total at follow-up[a]	–	–	–	–	19.1 (17.5)	–
SANS total at baseline[a]	–	53.1 (25.2)	–	–	53.7 (27.1)	–
SANS total at follow-up[a]	–	–	–	–	38.0 (24.0)	–
Intracranial volume (cm^3)[d]	1501.9 (150.4)	1499.8 (147.1)	0.983	1501.1 (158.3)	1482.2 (133.2)	0.774

Values represent mean (SD) unless otherwise stated. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] Data missing for some participants.
[b] Two patients were medication free at the time of scanning.
[c] Different typical and atypical antipsychotic dosages were converted into haloperidol equivalents using the guideline by Toru (2008).
[d] Age was used as a covariate for ANCOVA analysis.

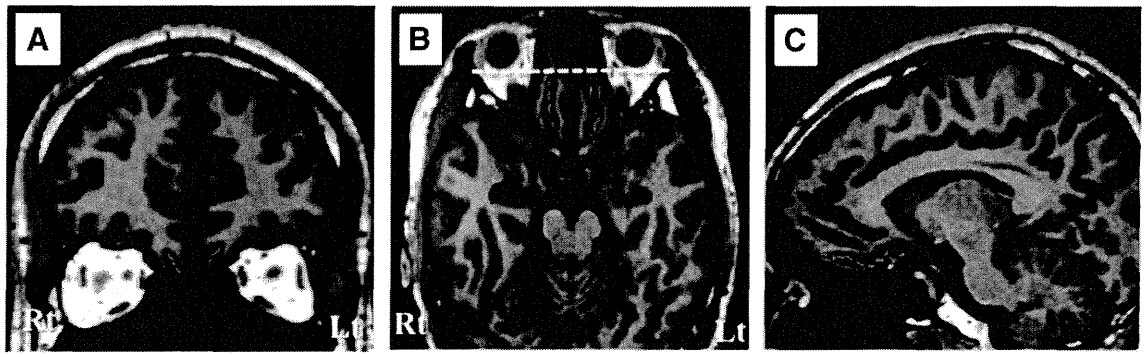

Fig. 1. Olfactory sulci on coronal (A), axial (B), and sagittal (C, left hemisphere) views, colored on 1-mm consecutive coronal slices. Panel A and the dotted line on panel B show the plane of the posterior tangent through the eyeballs (PPTE).

studies measured the sulcus depth by drawing a straight line (Huart et al., 2011; Rombaux et al., 2009), we traced the surface of the intrasulcal gray matter in order to reflect the contour of the sulcus into the measurement. The length of the sulcus in the anterior–posterior direction (mm) was equal to the number of these coronal slices. Intra- and inter-rater (TT and YN) intraclass correlation coefficients for the length and depth of the olfactory sulcus in 10 randomly selected brains were over 0.83.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. The average depth (sum of the depth in all slices containing the sulcus/slice number) and length of the olfactory sulcus at the baseline were analyzed using the repeated measures analysis of covariance (ANCOVA), with age and ICV as covariates, diagnosis and gender as between-subject factors, and hemisphere as a within-subject variable. The longitudinal changes in the sulcus depth and length were analyzed using repeated measures ANCOVA with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis and gender as between-subject factors, and time (baseline, follow-up) and hemisphere as within-subject variables. Post-hoc Scheffé's tests were used to follow-up these analyses.

The relationships between baseline measures of the olfactory sulcus and clinical variables were examined by Pearson's partial correlation coefficients controlling for age and ICV. The association between the annual change in the sulcus length and depth, which was calculated as [100×(measures at follow-up − measures at baseline)/measures at baseline]/inter-scan interval (year), and total SANS/SAPS scores (absolute score change between scans, score at follow-up) was examined using Spearman's rho due to the skewed distribution of these variables (tested by Kolmogorov–Smirnov tests). The association between the annual changes and cumulative dose of antipsychotics during scans was also analyzed using Spearman's rho. Statistical significance was defined as $p<0.05$.

3. Results

ANCOVA of the olfactory sulcus length showed no significant effect involving diagnosis (Table 2), but that for depth revealed significant main effects of diagnosis [F (1, 122) = 120.41, $p<0.001$] and hemisphere [F (1, 124) = 66.67, $p<0.001$] and an interaction between these factors [F (1, 124) = 9.04, $p=0.003$]. Post-hoc analyses showed that the olfactory sulcus depth was significantly shallower in the patients for both hemispheres ($p<0.001$) and deeper in the right hemisphere (controls, $p<0.001$; schizophrenia, $p=0.005$) (Fig. 2). These results did not change even when only the patients whose illness onset was within 1 year of baseline scanning ($N=48$) were included in the analyses, when we added medications (dose and duration) as covariates, or when we excluded the patients taking mood stabilizers ($N=4$). The patients who were receiving typical ($N=18$) and atypical ($N=43$) antipsychotics at baseline scanning did not differ significantly in their sulcus depth [F (1, 55) = 0.55, $p=0.463$]. We found significant effects of diagnosis [F (1, 35) = 47.27, $p<0.001$] and hemisphere [F (1, 37) = 14.30, $p<0.001$] in the baseline sulcus depth in our longitudinal sub-sample (20 patients and 21 controls), which were comparable to the results of the whole sample.

ANCOVA of the longitudinal analysis did not show either main effect of time for length [F (1, 37) = 0.23, $p=0.632$] or depth [F (1, 37) = 0.28, $p=0.600$], or any interaction involving time, showing no significant longitudinal changes in the sulcus morphology in either controls or schizophrenia patients (Fig. 3). We then examined possible longitudinal changes of the sulcus depth only in schizophrenia patients, but found no significant effect of time [F (1, 18) = 0.25, $p=0.619$; Scheffé's test, $p=0.588$].

Table 2
Olfactory sulcus measures.

	Baseline measures (mm)		Diagnosis effect	Change during follow-up (mm)[a]		Diagnosis × time interaction
	Controls	Schizophrenia		Controls	Schizophrenia	
	(N = 64)	(N = 64)		(N = 21)	(N = 20)	
Olfactory sulcus length			$F(1,122) = 1.67$, $p=0.198$			$F(1,37) = 0.43$, $p=0.514$
Left	41.6 (2.9)	42.3 (3.3)		0.0 (1.2)	0.0 (0.7)	
Right	42.1 (3.1)	42.4 (3.3)		−0.4 (1.3)	−0.2 (0.8)	
Olfactory sulcus depth			$F(1,122) = 120.41$, $p<0.001$			$F(1,37) = 1.26$, $p=0.268$
Left	13.4 (1.1)[b]	11.5 (1.4)		0.1 (0.4)	0.0 (0.3)	
Right	14.4 (1.1)[b,c]	12.0 (1.4)[d]		0.2(0.4)	−0.1 (0.5)	

Values represent mean (SD). [a]Negative value indicates a decrease in length. The statistical analyses reported here were based on repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable (see text). Post-hoc tests showed: [b]$p<0.001$, deeper than in schizophrenia; [c]$p<0.001$, deeper than in left hemisphere; and [d]$p=0.005$, deeper than in left hemisphere.

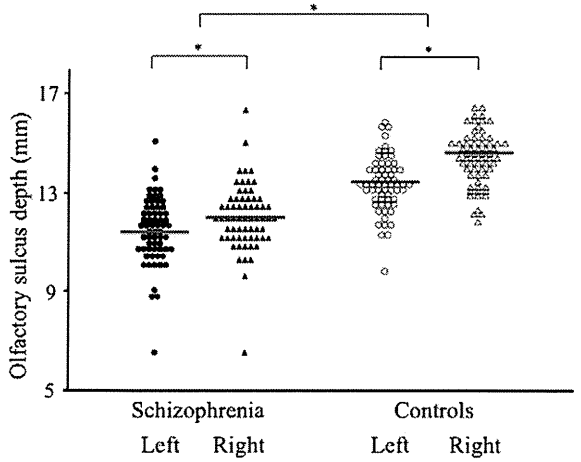

Fig. 2. Olfactory sulcus depth in the patients with schizophrenia and healthy controls at baseline. Horizontal lines indicate mean values. Post hoc Scheffé's test: *$p<0.01$.

The olfactory sulcus length and depth did not correlate with age in either group at the baseline. In the patients, the olfactory sulcus measures (baseline measures, annual change) did not significantly correlate with clinical variables [onset age, medication (dose, duration), illness duration, and total SANS/SAPS scores] after Bonferroni's correction for multiple comparisons. The sulcus length and depth were significantly correlated with each other only in the patients in the left hemisphere ($r=0.449$, $p<0.001$), but this relation was not significantly different from that of the controls ($p=0.267$, Fisher's z transformation).

4. Discussion

To our knowledge, this is the first MRI study to report olfactory sulcus morphology in first-episode schizophrenia with both cross-sectional and longitudinal designs. In the baseline comparison, the patients had a shallower olfactory sulcus compared with healthy controls bilaterally, while the sulcus length did not differ between the groups. In the longitudinal comparison, the sulcus length and depth did not change over time in either group. We did not find any significant relation between the sulcus morphology and clinical variables (e.g., onset age, medication, and symptom severity) in the patients. These findings suggest that altered depth, but not length, of the olfactory sulcus may be a static vulnerability marker of schizophrenia related to neurodevelopmental pathology.

Our baseline findings replicated and expanded the findings by Turetsky et al. (2009a) in showing that schizophrenia patients had abnormally shallow olfactory sulci, which could be due to a disturbance in olfactory system formation during neurodevelopment (Abolmaali et al., 2002; Hummel et al., 2003), even at the early illness stage. We also found a significant diagnosis-by-hemisphere interaction for the sulcus depth, supporting the concept that schizophrenia patients had a reduced normal right-sided lateralization of the olfactory sulcus depth (Turetsky et al., 2009a). Nguyen et al. (2011) did not find altered olfactory sulcus depth on PPTE slices in chronic schizophrenia, but this single-slice approach using external landmarks (i.e., eyeballs) may be partly biased by subtle brain tilt and/or the positional relation between the eyeballs and brain. The present and previous (Turetsky et al., 2009a) MRI findings based on the entire sulcus measures are consistent with the notion that olfactory dysfunction, which exists in the first-episode or prodromal phase of schizophrenia (Brewer et al., 2001, 2003), as well as in the patients' first-degree relatives (Kamath et al., in press), may be a sensitive indicator of schizophrenia pathology and may even serve as an early warning sign of disease vulnerability or onset (Turetsky et al., 2009b). Given the recent neuroimaging evidence suggesting that brain morphologic changes, including abnormalities in sulcogyral pattern (Yucel et al., 2003), predate the onset of psychosis (Fusar-Poli et al., 2011; Smieskova et al., 2010), the olfactory sulcus morphology in high-risk subjects for developing psychosis and its possible relation to clinical characteristics (e.g., severity of prodromal symptoms, later transition into psychosis) seem worthy of examination in future studies.

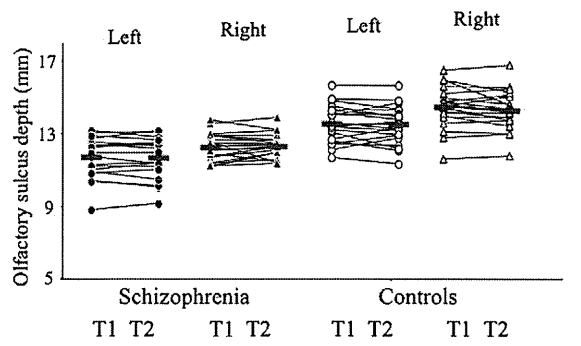

Fig. 3. Scatterplots of absolute olfactory sulcus depth in the patients with schizophrenia and healthy controls. Values of baseline (T1) and follow-up scan (T2) in each subject are connected with a straight line. Horizontal lines indicate means of each group.

On the other hand, dynamic brain changes, including excessive cortical thinning (van Haren et al., 2011) or gray matter reduction (Mane et al., 2009) over time in the frontal area, may also occur during or after the onset of schizophrenia (Pantelis et al., 2007). Interestingly, a shallow olfactory sulcus (Wang et al., 2011) and olfactory dysfunction (Mesholam et al., 1998) have also been reported in neurodegenerative diseases such as Parkinson's disease, although the pathological mechanism is unknown. However, the present longitudinal analyses demonstrated no progressive changes in the olfactory sulcus measures in either first-episode schizophrenia or controls. Antipsychotic medication can significantly affect brain morphology (reviewed by Moncrieff and Leo, 2010), especially regarding progressive brain changes (Takahashi et al., 2010; van Haren et al., 2011) in schizophrenia, but we did not find any medication effect on the length and depth of the olfactory sulcus. Our longitudinal analyses thus revealed that olfactory sulcus morphology may be static, at least during the early illness stage of schizophrenia.

Given that olfactory sulci on the human orbitofrontal cortex appear at 16 weeks gestation and are prominent at 25 weeks (Chi et al., 1977), our results offer a clue regarding the estimation of gestational age at which neurodevelopmental insults occur in schizophrenia. On the basis of gyral development of the human brain (Chi et al., 1977; Garel et al., 2001), previous findings of abnormal cingulate cortex folding in schizophrenia (Fujiwara et al., 2007; Yucel et al., 2002) also suggest neurodevelopmental disturbance by the third trimester of gestation, whereas the orbital sulci, which are not recognizable until 36 weeks of gestation, are of a normal depth in patients (Turetsky et al., 2009a). Our own results of midline brain structures in schizophrenia (Takahashi et al., 2008a,b) partly parallel these findings; abnormally small adhesio interthalamica that develops during early gestation (Rosales et al., 1968) and normal cavum septi pellucidi (CSP), which is related to fusion of the septum pellucidi within 3–6 months of birth (Shaw and Alvord, 1969), support the idea that schizophrenia is more closely related to aberrant neurodevelopment early in gestation. Since discrepant findings, such as altered orbital sulcus pattern (Nakamura et al., 2007; Takayanagi et al., 2010) and increased prevalence of large CSP (Trzesniak et al., 2011), have been also reported in schizophrenia, further comprehensive assessment of these potential neurodevelopmental markers in the same cohort of schizophrenia patients is required in future studies ideally in various illness stages (including prodromal phase).

A few possible confounding factors in this study should be taken into account. First, although our findings on altered depth of the olfactory sulcus may reflect embryonic disruption of the olfactory system, we did not assess olfactory function or other olfactory structures. Reduced olfactory bulb volume in schizophrenia patients (Nguyen et al., 2011; Turetsky et al., 2000) and in first-degree relatives (Turetsky et al., 2003) suggests its significant role in the neurodevelopmental pathology of schizophrenia. The olfactory bulb can be well identified on T2-weighted MR images (Duprez and Rombaux, 2010; Rombaux et al., 2009), but our T1-weighted images did not allow reliable measurement of the bulb. Also, we could not reliably assess the average depth of the orbital sulci because of their variability and complexity (Chiavaras and Petrides, 2000). Second, some of our first-episode patients had been psychotic for several years and already received substantial amounts of antipsychotics at baseline scanning owing to our definition of the first-episode. Although the results did not change even when we included only the patients whose illness duration is $\leq$1 year in the analyses and we did not find any effect of medication on the sulcus morphology in our sample, the patients with shorter illness duration and/or medication naïve patients should be examined in the future. Third, although we found no relation between the olfactory sulcus morphology and symptom severity at scanning, the possibility exists that it relates to an even later clinical course of schizophrenia. Finally, given that olfactory dysfunction may help to discriminate among various psychiatric disorders as discussed by Nguyen et al. (2011), disease specificity of the olfactory sulcus abnormalities is worthy of further examination.

5. Conclusion

The present study demonstrated a shallow olfactory sulcus in schizophrenia, which already existed in first-episode patients, and this showed no active progressive changes after the illness onset. Our results, as well as the time point at which the sulcus develops during the gestation period, suggest that the olfactory sulcus depth could be a marker of early neurodevelopmental abnormalities in schizophrenia.

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Brief report

Longitudinal MRI study of the midline brain regions in first-episode schizophrenia

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ABSTRACT

This magnetic resonance imaging (MRI) study investigated the prevalence and size of the adhesio interthalamica (AI) and cavum septi pellucidi (CSP) in 64 first-episode schizophrenia patients and 64 controls, of whom longitudinal data were available for 20 patients and 21 controls. The AI was shorter in the patients and showed longitudinal decline in both groups; there was also a trend for AI atrophy to correlate with negative symptoms. The CSP showed no group difference. These results suggest a role for the AI as a possible neurodevelopmental marker of schizophrenia.

1. Introduction

The adhesio interthalamica (AI), a midline structure connecting the medial surfaces of the thalami, is variable in size among individuals and missing in about 20% of human brains (Carpenter and Sutin, 1983). Previous neuroimaging studies have demonstrated that schizophrenia patients are more likely to have a smaller AI (reviewed by Trzesniak et al., 2011a), possibly reflecting early developmental abnormalities. A large cavum septi pellucidi (CSP) ($\geq$6 mm; Takahashi et al., 2007), which is formed by the incomplete fusion of the septum pellucidi (Rakic and Yakovlev, 1968), may also be related to fetal neurodevelopmental abnormalities in schizophrenia (Trzesniak et al., 2011b). Our previous magnetic resonance imaging (MRI) studies showed smaller AI and a higher rate for it to be absent, but no difference in the size and prevalence of CSP, in a large sample of chronic schizophrenia patients compared with controls (Takahashi et al., 2007, 2008a), but these results may have been partly biased by the effects of medication and illness chronicity. A recent longitudinal MRI study demonstrated the possibility that the size of these midline regions could change during the course of the illness (Trzesniak et al., 2012), whereas Davidson et al. (2012) reported longitudinal stability in the CSP length in first-episode schizophrenia.

This MRI study aimed to replicate our earlier observations described above in a cohort of first-episode schizophrenia and to investigate the changes over time in the size of these midline regions. Given their potential role as neurodevelopmental markers, we posited no diagnosis-by-time interaction in these regions.

2. Methods

2.1. Participants

Sixty-four schizophrenia patients fulfilling the ICD-10 research criteria (World Health Organization, 1993), whose illness duration was 1 year or less (n=48) or under first psychiatric hospitalization (n=16), were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. Sixty-four healthy volunteers were recruited from the community, hospital staff, and university students. The controls were given a questionnaire consisting of 15 items concerning their personal and family histories of illness; none had a personal or family history of psychiatric illness among their first-degree relatives. All subjects were right-handed and physically healthy, and did not have any history of serious head trauma, neurological illness, substance abuse, or serious medical disease. Of the 128 participants, 37 patients and 60 controls were included in our previous cross-sectional studies of the CSP (Takahashi et al., 2007) and AI (Takahashi et al., 2008a). Follow-up MRI data were available for 20 patients and 21 controls; the characteristics of this sub-sample were largely comparable with those of the whole sample of this study (Table 1). The controls were also assessed using the questionnaire at follow-up to ensure that none had any neuropsychiatric disorder during the period between scans.

The patients' clinical symptoms were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative and Positive Symptoms (SANS/SAPS; Andreasen, 1984). The diagnosis of schizophrenia was confirmed in all patients at least 6 months after the illness onset based on

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Table 1
Sample characteristics and brain measurements of the participants.

	Cross-sectional sample			Longitudinal sample		
	Controls	Schizophrenia	Group comparisons	Controls	Schizophrenia	Group comparisons
Male/female	37/27	37/27	Chi-square=0.00, p=1.000	13/8	14/6	Chi-square=0.30, p=0.585
Age (years)	25.1 ± 5.0	24.0 ± 4.7	F (1, 126)=1.64, p=0.203	24.5 ± 5.0	23.8 ± 5.0	F (1, 39)=0.19, p=0.664
Height (cm)	167.0 ± 7.5	164.9 ± 7.6	F (1, 126)=2.60, p=0.109	167.3 ± 7.6	166.2 ± 6.6	F (1, 39)=0.27, p=0.606
Education (years)	16.5 ± 2.6	13.5 ± 1.9	F (1, 126)=57.55, p < 0.001	15.6 ± 2.4	13.0 ± 1.6	F(1, 39)=17.24, p < 0.001
Parental education (years)[a]	13.2 ± 2.5	13.0 ± 2.0	F (1, 124)=0.50, p=0.482	12.8 ± 2.6	12.5 ± 2.1	F (1, 39)=0.10, p=0.756
Inter-scan interval (years)	–	–		2.5 ± 0.4	2.7 ± 0.8	F (1, 39)=1.30, p=0.261
Onset age (years)	–	23.1 ± 4.7	–	–	22.7 ± 5.1	–
Illness duration at baseline (months)	–	11.2 ± 12.2	–	–	10.2 ± 9.4	–
Medication type (T/AT/mixed)						
At baseline	–	18/43/1[b]	–	–	6/12/2	–
During follow-up	–	–	–	–	3/13/4	–
Medication dose (haloperidol equivalent)						
At baseline (mg/day)	–	10.3 ± 8.8	–	–	14.6 ± 11.7	–
Cumulative dose during follow-up (mg)	–	–	–	–	9852 ± 8727	–
Duration of medication at baseline (months)	–	8.3 ± 12.6	–	–	8.3 ± 10.1	–
SAPS total at baseline	–	27.3 ± 21.9 (N=61)	–	–	33.0 ± 24.0 (N=17)	–
SAPS total at follow-up	–	–	–	–	19.1 ± 17.5 (N=19)	–
SANS total at baseline	–	53.1 ± 25.2 (N=61)	–	–	53.7 ± 27.1 (N=17)	–
SANS total at follow-up	–	–	–	–	38.0 ± 24.0 (N=19)	–
AI absent [N (%)]	7 (10.9)	10 (15.6)	Chi-square=0.61, p=0.435	3 (14.3)	4 (20.0)	p=0.627, Fisher's exact test
AI length at baseline (mm) (median)	8.9 ± 3.5 (10.0)	7.3 ± 3.2 (7.0)	F (1, 122)=11.08, p=0.001	8.4 ± 3.5 (8.0)	6.9 ± 3.3 (6.5)	F (1, 35)=1.40, p=0.245
AI length at follow-up (mm) (median)	–	–	–	8.1 ± 3.4 (7.0)	6.8 ± 3.1 (6.5)	F (1, 35)=1.71, p=0.200
AI change during follow-up (mm)[c]	–	–	–	−0.3 ± 0.6	−0.2 ± 0.7	F (1, 33)=1.39, p=0.247
large CSP [N (%)]	8 (12.5)	3 (4.7)	p=0.115, Fisher's exact test	2 (9.5)	1 (5.0)	p=0.578, Fisher's exact test
CSP length at baseline (mm) (median)	4.7 ± 10.1 (2.0)	3.1 ± 6.5 (2.0)	F (1, 122)=0.26, p=0.611[d]	4.8 ± 11.4 (2.0)	3.4 ± 5.9 (2.0)	F (1, 35)=0.00, p=0.970[d]
CSP length at follow-up (mm) (median)	–	–	–	4.9 ± 11.6 (2.0)	3.2 ± 5.7 (2.0)	F(1, 35)=0186, p=0.669[d]
CSP change during follow-up (mm)[c]	–	–	–	+0.1 ± 0.5	−0.2 ± 0.7	F (1, 33)=0.10, p=0.753
Intracranial volume (cm^3)	1501.9 ± 150.4	1499.8 ± 147.1	F (1, 125) < 0.01, p=0.983	1501.1 ± 158.3	1482.2 ± 133.2	F (1, 38)=0.08, p=0.774

Values represent means ± S.D.'s unless otherwise stated.
AI, adhesio interthalamica; AT, atypical; CSP, cavum septum pellucidum; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; T, typical.

[a] Data missing for one control and one schizophrenia subjects.

[b] Two patients were medication free at the time of scanning.

[c] Negative value indicates a decrease in length. The statistical analyses reported herein were based on repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable (see text). The main effect of time was F (1, 37)=4.95, p=0.032 for the AI and F (1, 37)=0.02, p=0.883 for the CSP.

[d] The CSP measures were log-transformed for statistics because of their skewed distribution (p < 0.01, Kolmogorov–Smirnov test). The skewness and kurtosis statistics of baseline CSP length were 4.82 and 24.12 before transformation and 1.00 and 2.49 after transformation, respectively.

information obtained from a detailed chart review. Other clinical information, including cumulative neuroleptic dosage during the study, was also collected in this chart review. Medication and other clinical data are summarized in Table 1.

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

2.2. Magnetic resonance imaging procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160-180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm^3. The follow-up data were acquired using the same scanner/parameters as described above. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

To assess the AI and CSP, the images were processed using Dr. View software (AJS, Tokyo, Japan) as described elsewhere (Takahashi et al., 2007, 2008a). Briefly, brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure (AC-PC) line. One rater (TT), who was blind to the subjects' identity and time of scan, counted the number of coronal slices where each midline region was clearly seen. The length of the AI and CSP (in mm) was equal to the number of these slices. We considered the AI as present when it could be identified on three or more slices on both coronal and axial views (Takahashi et al., 2008a). A CSP equal to or greater than 6 mm was defined as large on the basis of previous reports (e.g., Nopoulos et al., 1997; Kwon et al., 1998; Kasai et al., 2004). Intra- and inter-rater (TT and KN) intraclass correlation coefficients for the AI and CSP lengths (n=30) in randomly selected brains were over 0.97.

2.3. Statistical analysis

Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used to assess the frequency of the AI and large CSP. The length of each

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midline region was analyzed using analysis of covariance (ANCOVA), with intracranial volume (ICV) and age as covariates and with diagnosis and gender as between-subject factors. Gender was used as a between-subject factor on the basis of possible gender effect on the AI size (Allen and Gorski, 1991). The CSP measures were log-transformed because of their skewed distribution (eFig. 1, Table 1). Longitudinal changes were analyzed using repeated measures ANCOVAs with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis and gender as between-subject factors, and time (baseline, follow-up) as a within-subject variable. Post-hoc Scheffé's tests (Scheffé, 1959) were used to follow up these analyses. The relationships between the midline regions (baseline length, absolute length change during scans) and clinical variables were examined by Pearson's partial correlation coefficients controlling for age and ICV. Inter-scan interval and cumulative medication dose were also used as controlling factors for correlational analyses between length change and clinical variables. Statistical analyses reported here were performed using the STATISTICA software package (Statsoft, Tulsa, OK); the statistical modeling was based on its manual (Statsoft, 1994) as in our previous publications (e.g., Takahashi et al., 2009). Statistical significance was defined as $p < 0.05$.

3. Results

There was no group difference in the prevalence of an absent AI (Table 1), but ANCOVA of the baseline AI length revealed significant main effects for diagnosis [$F(1, 122)=11.08$, $p=0.001$] and gender [$F(1, 122)=5.36$, $p=0.022$] but not their interaction. Post hoc analyses showed that the patients had a shorter AI than controls ($p=0.004$) (eFig. 2) and males had a shorter AI than females ($p < 0.001$). However, the main effect for diagnosis was not significant when we added medication duration and dose also as covariates [$F(1120)=1.20$, $p=0.276$]. Longitudinal analyses of the AI revealed a significant effect of time [$F(1, 37)=4.95$, $p=0.032$], but no diagnosis-by-time interaction, indicating its atrophy over time in both groups ($p=0.032$). The AI length, but not CSP length, at the baseline was negatively correlated with age for both controls ($r=-0.343$, $p=0.005$) and patients ($r=-0.277$, $p=0.027$). In the patients, the AI length was not correlated with the onset age, illness duration, medication (duration and dose), or total SANS/SAPS scores. The cumulative medication dose did not correlate with the AI change over time. Overall, although not statistically significant [$n=16$, $F(1,15)=2.34$, $p=0.147$], negative symptoms (total SANS score) reduced over time (Table 1), but greater AI atrophy over time was correlated at a trend level with less improvement in negative symptoms ($r=0.619$, $p=0.032$), though this did not survive Bonferroni correction (Dunn, 1961).

For the CSP (length and prevalence), we found no effect of diagnosis, time, or gender (Table 1, eFig. 1). The CSP categories (absent, present, or large) changed during follow-up in one control [from absent to present (1 mm)] and one patient [from present (2 mm) to absent]. The CSP length did not correlate with any clinical variables.

The ANCOVA results of length change over time remained the same for both AI and CSP even when we added baseline medication dose or deleted cumulative medication dose as the covariate.

4. Discussion

Consistent with previous findings in first-episode schizophrenia (Trzesniak et al., 2012) or clinical high-risk subjects (Takahashi et al., 2008b), baseline results in this study demonstrated shorter length of the AI in schizophrenia patients in the early illness stages. A lack of correlation with medication and illness duration, as well as no disease-specific progressive changes, also supports the concept that AI malformation may at least partly represent early neurodevelopmental disturbance in schizophrenia (Weinberger, 1987). On the other hand, we did not identify any differences in the CSP measures between the groups, suggesting that it may not play a major role in the neurobiology of schizophrenia (Takahashi et al., 2007, 2008c).

The present study and a previous (Trzesniak et al., 2012) longitudinal analysis found AI atrophy over time in both schizophrenia and controls, supporting the notion that the AI develops during early gestation, but also undergoes increasing atrophy with age (Rosales et al., 1968; O'Rahilly and Müller, 1990). This study also replicated that men had shorter AI than women (Allen and Gorski, 1991). While the functional significance of the AI, as well as the nature of its atrophy, remains unclear, the midline nuclei of the thalamus including the AI have efferent connections with the amygdaloid nuclei (Graff-Radford, 1997) and are involved in the regulation of the dopamine release of the basal ganglia (Romo et al., 1984). A trend-level correlation between longitudinal AI atrophy and negative symptoms may support a relationship between AI abnormalities and negative symptoms in schizophrenia (Meisenzahl et al., 2000, 2002; Takahashi et al., 2008a), but this effect needs to be replicated. Also, this possible correlation would suggest a role in schizophrenia for accelerated atrophy in AI during adulthood in addition to the hypothesized role as an early neurodevelopmental marker. Although we found no diagnosis-by-time interaction in AI length, it is possible that the reduced AI length apparent at the first episode is due to accelerated AI atrophy at or before illness onset and our sample size or duration is underpowered to examine this effect.

The present study supported the role of the AI as a neurodevelopmental marker of schizophrenia, although possible medication effect on the AI morphology should be further examined. In addition, our longitudinal analyses should be considered preliminary due to the small sample size. For example, in contrast to the negative CSP findings in this study, several previous studies have found CSP abnormalities in schizophrenia (reviewed by Trzesniak et al., 2011b) and Trzesniak et al. (2012) demonstrated significant expansion of the CSP in 52 first-episode patients even during a shorter follow-up period (18 months). As Choi et al. (2008) reported abnormal CSP in subjects at risk for psychosis using the CSP grading system, which integrated CSP length, width, and overall size, the possibility also exists that measuring only the length of the CSP might not be a sensitive enough approach to detect existing changes of the CSP. Another limitation of this study is that neighboring structures are not measured, so it cannot be ruled out that differences in AI are accounted for by differences in thalamic or ventricular volume or orientation. Additional longitudinal studies in a larger cohort in various illness stages (e.g., prodromal and chronic phases) are required to further understand the nature of midline brain abnormalities in the course of schizophrenia.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.12.001.

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Gray matter changes in subjects at high risk for developing psychosis and first-episode schizophrenia: a voxel-based structural MRI study

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Objectives: The aim of the present study was to use a voxel-based magnetic resonance imaging method to investigate the neuroanatomical characteristics in subjects at high risk of developing psychosis compared with those of healthy controls and first-episode schizophrenia patients.

Methods: This study included 14 subjects with at-risk mental state (ARMS), 34 patients with first-episode schizophrenia, and 51 healthy controls. We used voxel-based morphometry with the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra tools to investigate the whole-brain difference in gray matter volume among the three groups.

Results: Compared with the healthy controls, the schizophrenia patients showed significant gray matter reduction in the left anterior cingulate gyrus. There was no significant difference in the gray matter volume between the ARMS and other groups.

Conclusion: The present study suggests that alteration of the anterior cingulate gyrus may be associated with development of frank psychosis. Further studies with a larger ARMS subjects would be required to examine the potential role of neuroimaging methods in the prediction of future transition into psychosis.

Keywords: schizophrenia, psychosis, high risk, MRI, cingulate gyrus

INTRODUCTION

Neuroimaging studies have demonstrated subtle but widespread brain structural alterations, such as volume reduction of fronto-temporo-limbic regions as well as enlarged lateral and third ventricles, in first-episode schizophrenia (Steen et al., 2006; Vita et al., 2006; Ellison-Wright et al., 2008), which are not due to illness chronicity and antipsychotic medication. Recent prospective longitudinal magnetic resonance imaging (MRI) studies, including our own data showing progressive gray matter reduction of the temporal region (approximately 2–3% per year) (Takahashi et al., 2010, 2011), further revealed progressive brain structural change and its relationship to clinical course or outcome in first-episode schizophrenia (Andreasen et al., 2011). These longitudinal findings might be consistent with the clinical observation that a long duration of untreated psychosis (DUP), which could lead to severe brain pathological changes during the early illness stage (Lappin et al., 2006; Takahashi et al., 2007), is related to poor outcome of schizophrenia patients (Marshall et al., 2005; Perkins et al., 2005). Examining potential neurobiological markers that predate the onset of psychosis might lead to appropriate early intervention and thus prevent deterioration of social function and the progression of structural brain alterations.

It is not yet clear at which illness stage brain abnormalities occur in schizophrenia. Subjects with at-risk mental state (ARMS), who exhibit prodromal-like symptoms and have an increased risk of developing psychosis (Yung et al., 2003), might share disease vulnerability as well as brain morphological changes with patients with overt schizophrenia. Subjects with ARMS are heterogeneous on the basis of their outcome, as only about 36% of them develop psychosis during 3-year follow-up (Fusar-Poli et al., 2012). Previous MRI studies using voxel-based morphometry (VBM), which allows automated whole-brain analysis, revealed more severe gray matter reduction predominantly in the fronto-temporo-limbic regions in ARMS subjects with later transition than in those without (Pantelis et al., 2003; Borgwardt et al., 2007; Fusar-Poli et al., 2011). More specifically, Fornito et al. (2008) revealed that baseline differences in the anterior cingulate cortical thickness distinguished between ARMS with and without later transition, but they did not directly compare ARMS subjects and patients with overt psychosis.