褶曲パターンは発達早期にほぼ決定されるので，gyrification index 増大の所見[7]や，左前部帯状回の脳溝の分枝(傍帯状溝)が減少し，左半球優位性が失われているという所見[8]は，比較的早期の神経発達障害を示唆する固定的変化と考えられるであろう．以上の所見から，病前には早期神経発達障害による大脳半球間あるいは半球内の機能的結合の変化が生じていることが示唆される．

病前の状態をうかがい知るには，統合失調症患者の親族，すなわち遺伝的ハイリスクの状態にある人を対象とした研究が参考になる．第1〜2度親族に少なくとも2人の罹患者をもつ青年を前方視的に追跡するエジンバラハイリスク研究は，この集団における統合失調症の発症率が10年間で約10%と推定されることから，従来の遺伝的ハイリスク研究に比較して病前の状態にある対象を多く含むといえる．この研究プロジェクトからは，ハイリスク者における左側の扁桃体-海馬複合体および両側視床の体積減少[9]，両側の前部帯状回の灰白質減少[10]が報告されている．しかし，遺伝負因の強いサンプルは一般の統合失調症患者とは異なった特徴を有する可能性がある．親族を対象とした体積測定研究のメタ解析では，海馬あるいは扁桃体-海馬複合体の体積減少がもっとも一致した所見とされる．このように親族の研究からは海馬体積の減少が脆弱性を形成すると考えられ，統合失調症の神経発達障害モデルとして古くから検討されている新生仔期腹側海馬傷害ラット[11]の根拠にもなっている．

統合失調症スペクトラムからみた統合失調症の発症機構と防御因子

統合失調型障害(schizotypal disorder)は軽度なあるいは萌芽的な統合失調症様症状を特徴とし，明らかで持続的な精神病(陽性)症状を示さない．統合失調型障害は統合失調症患者の親族に多く認められ，症候学的および遺伝的に統合失調症スペクトラムの一部を形成していると考えられている．統合失調症の発症に先行して認められることもあり，その場合は前駆状態としてとらえることができるが，多くは症状を呈しながらも長期間比較的安定した状態を保つようである．すなわち統合失調型障害は，統合失調症への脆弱性を有しながらも顕在発症から防御されているという，二面性をもった状態といえる．

このような統合失調型障害と統合失調症に共通する神経生物学的特徴は，統合失調症スペクトラムに共通して存在する脆弱性にかかわる変化を表すと考えられる．また両者の相違点からは，統合失調症の発症，すなわち精神病症状顕在化の脳内機序を明らかにできる可能性がある．逆に，統合失調型障害の病態生理を明らかにすることは顕在発症を防御する脳機構についての示唆を与えるであろう．著者らは上記のような観点から，MRIにより統合失調型障害患者と統合失調症患者の脳形態の包括的な比較検討を行った．その結果はすでに公表済みであるので，以下にそこから考えられる統合失調症の脆弱性と発症にかかわる脳機構について概略を述べる．

扁桃体，海馬，上側頭回(とくに後方部分)などの体積減少は，統合失調型障害と統合失調症に共通して認められた[12,13]ことから，脆弱性を表す変化であることが示唆される．海馬および扁桃体については，前述の遺伝的ハイリスク者における所見と一致している．これに対して前頭前野は統合失調症では広範囲に体積減少が認められたのに対し，統合失調型障害ではむしろ体積の増大を示した[12]．

これらの所見から統合失調症においては前頭前野による他の脳領域への抑制的調節の減退により側頭葉の変化が臨床的に顕在化し，精神病症状として発現しているという病態生理が想定できるのではなかろうか(図1)．それにより，これまでに多くの研究が上側頭回や内側側頭葉の体積減少と幻覚・妄想，陽性の思考形式障害など陽性症状の重症度との相関を示していることを説明できるかもしれない．

統合失調症の縦断的経過において，このような病態生理が成立することを説明しようとするのが，倉知による側頭-前頭2段階発症仮説[14]であるが，それを検証するには統合失調症の発症前後における縦断的追跡研究が必要である．また，統合失調症型障害において前頭前野の体積がむしろ増大していたことは，統合失調症発症に対する防

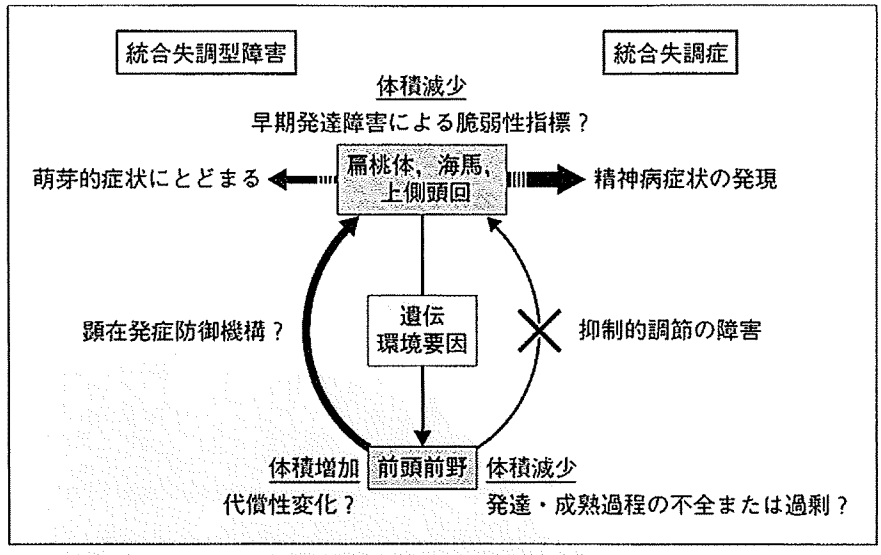

図 1　脳形態からみた統合失調症の発症機構と，統合失調型障害における防御因子[15]

御因子と関連するかもしれず[15]，興味深い所見と思われる(図 1)．

統合失調症前駆期の脳形態変化

統合失調症における脆弱性にかかわる偏倚と発症に関連する異常を明らかにするには，前駆期における特徴を検討し，縦断的追跡により顕在発症に至った後の状態と比較することがもっとも直接的で有効なストラテジーであるかもしれない．近年では，統合失調症を含む精神病性障害に対する早期介入活動の新しい試みと軌を一にして，初回エピソード，さらにさかのぼって前駆期における脳形態変化も検討されるようになってきた．実際には前駆症状を示す段階で確定診断はできないので，特定の徴候を有する者を操作的に精神病発症リスクの高い状態(at risk mental state：ARMS)と診断して検査対象とする[16]．しかし，ARMS と診断された者が 1〜2 年以内に精神病に移行する率は 30〜40%と報告されており，かなりの率で偽陽性が存在すると考えられる．そのため，真の前駆期の特徴を知るためには，ARMS と診断された者を追跡し，発症に至った者の所見を吟味しなければならない．また，注意すべき点として，ARMS から精神病に移行する場合かならずしも統合失調症を発症するとは限らず，精神病症状を伴う気分障害など多様な疾患を発症しうる．ARMS から統合失調症を発症した者を十分な数だけそろえた縦断的研究はまだない．

1. 後に精神病を発症したARMSにおける所見

この分野において先進的な研究を推進しているメルボルン大学のグループは，ARMS のうち後に精神病を発症した者では発症していない者と比較して，ARMS の時点で右の海馬・海馬傍回，上側頭回，下前頭回および両側帯状回の灰白質が減少していることを報告した[17]．バーゼル大学の検討では，ARMS において後部帯状回，楔前部，左の島回，上側頭回，海馬，扁桃体，右の側頭葉前方部の灰白質が健常対照群より減少していた[18]．また，後に統合失調症を発症した者では発症しなかった者より右の島回，上側頭回前方部，前部帯状回の灰白質が減少していた．これら複数のサンプルによる研究結果は，前駆状態においてすでに脳灰白質の減少がある程度存在すること，それは同様の前駆症的症状を示しながら発症しない，あるいは発症までより長期間を要する者に比較して顕著であることを示している．

2. 精神病発症前後の縦断的所見

メルボルングループによる最初の報告[17]によると，後に精神病に移行した ARMS において，発症前後の縦断的比較により左の海馬傍回・紡錘状回，眼窩前頭葉，小脳，両側の帯状回に進行性の灰白質減少がみられた．移行しなかった群では右小脳に灰白質減少がみられたのみであった．その後，脳表面の微細な経時的収縮を解析する方法に

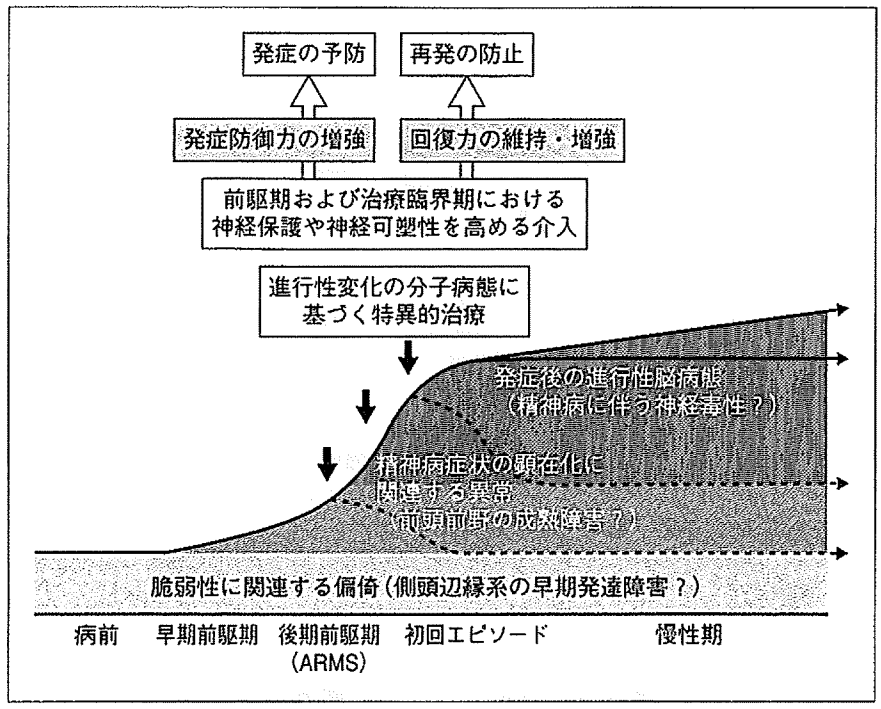

図 2　統合失調症の縦断的経過において想定される神経生物学的変化と早期介入の将来展望

より，後に精神病に移行した ARMS では前頭前野により顕著な収縮が認められたこと[19]や，上側頭回の詳細な解析により明らかな進行性灰白質体積減少が生じたこと[20]も報告されている．なお，メルボルングループは多数例の海馬と扁桃体の体積を横断的に比較し，ARMS の海馬と扁桃体体積は精神病への移行の有無にかかわらず健常人と有意差がないが，初回エピソード統合失調症患者では左側の，慢性統合失調症患者では両側の海馬体積が減少していたと報告している[21]．この所見は海馬における発症後の進行性変化を示唆しており，前述の遺伝的ハイリスクや統合失調症スペクトラムにおける所見と一致していない．

バーゼルのサンプルでは，統合失調症を発症した ARMS において発症前後の比較により右の眼窩回，左の直回，右の下側頭回，上前頭回，上頭頂小葉，左の楔前部，右の小脳の灰白質体積減少が報告されている[22]．また，ARMS 基準を用いた研究ではないが，前述のエジンバラハイリスク研究において一過性の精神病症状を示した遺伝的ハイリスク者のうち，経過観察中に統合失調症を発症した症例における縦断的検討により，左の下側頭回，鉤回，右の小脳において灰白質の進行性減少が認められた[23]．

上記の所見は，前駆期においてすでに進行性の脳形態変化が生じていることを一致して示している．顕在発症が切迫した状態では，精神病性障害の基準を満たしていなくとも脳内ではすでに発症に関連する病的変化が生じているのかもしれない．

脆弱性から発症予防へ

これまでみてきたように，統合失調症における脳形態の異常は，発症前から存在すると考えられる固定的な部分は比較的軽微であり，むしろ発症前後から活発に生じる進行性変化によって明らかになるようである．本稿では触れていないが，発症後早期の初回エピソードの時期にも，発症の前後と同様に活発な進行性形態変化が起こることが報告されている．最近の双生児研究からは，脳形態の進行性変化も一部は遺伝的要因によるものであることが示唆されているが，一方でそれはかなり可変的なものと考えられる．Cannabis は統合失調症の発症を促進し[2]，脆弱性を高める作用をもつと考えられるが，cannabis 乱用自体が海馬の萎縮を引き起こすこと[24]や，初回エピソード統合失調

症患者における進行性脳体積減少を加速させること[25]が報告されている．また，第二世代抗精神病薬が初回エピソード患者における脳体積減少の抑制[26]や脳体積増加[27]をもたらすことを示唆する報告もある．

脆弱性について解明する臨床的意義のひとつは，脆弱性をもった個体における発症予防の実現に資することであろう．その際に早期治療の標的となるのは，発症前から存在する脆弱性そのものではなく，脆弱性とは区別される疾患自体と関連する変化であり，それをいかに最小限に抑えるかが重要と考えられる(図2)．統合失調症の場合は上で述べたような発症前後から活発に生じる進行性変化の防止を治療目標とすることが，発症予防を含めた予後の改善につながる可能性があるが，いまのところ実証的データはない．統合失調症の予防の実現のためには，進行性変化の分子病態解明に基づく特異的治療法の開発が大きな目標となるであろう．しかし，神経保護作用をもつ薬物や，認知訓練や認知行動療法の効果も，非特異的であっても発症に対して抑制的に作用する可能性がある．そのような検討を，背景機序としての脳の構造や機能の変化を評価しながら進めていくことも有意義と思われる．

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統合失調症の早期介入・初期治療と予後

Early intervention and prognosis in schizophrenia

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要約

統合失調症においては，精神病未治療期間(DUP)が長いと転帰が不良であるという多くの報告がある。予後を改善するためには，初回エピソードにおいて，より早期に適切な治療を開始することが重要である。また発症からの数年間は臨床症状や社会機能の悪化，再発などが生じやすく，長期予後を左右する治療臨界期と考えられ，より重点的な介入が求められる。近年では，精神病発症高リスク状態(ARMS)，すなわち前駆期が疑われる状態に対する介入研究も行われているが，まだ未解明の課題が多い。脳構造画像研究によって，主として前駆期から初回エピソードに生じる進行性脳病態が示唆されており，早期介入の重要性を支持するものである。またこれを，長期予後改善のための治療標的として検討することも重要と考えられる。

Key Words 精神病未治療期間(DUP)，治療臨界期，初回エピソード，精神病発症高リスク状態(ARMS)，進行性脳病態

はじめに

近年，統合失調症への早期介入が国際的に活発化し，わが国でも注目されている。その主要目標はいうまでもなく長期予後の改善である。早期介入は，精神病症状(陽性症状)が顕在化してからの初回エピソードにおける介入と，前駆期における介入に分けられる。前駆期と初回エピソードは本来連続的なものであるが，実践場面では別々の臨床病期として異なる対応が求められる。以下に早期介入による予後改善のエビデンスと可能性についてまとめてみたい。

1 初回エピソードにおける早期介入と精神病未治療期間(DUP)

1．DUPと臨床的転帰

疾患としての例にもれず，統合失調症においても早期発見・早期治療が重要である第一の根拠は，精神病未治療期間(duration of untreated psychosis；DUP)，すなわち最初の精神病症状が明らかになってから，適切な抗精神病薬治療が開始されるまでの期間が予後の決定因子であるということである。DUPと臨床的転帰との関連については数多くの報告があり，2005年に発表された2つのメタ解析[1)2)]の結果も，それを支持するものとなっている。

DUPが長いとベースライン(治療開始時)の陰性症状

が強い[2]。図1に示されるように，6～24ヵ月後には陰性症状，陽性症状，Quality of Life，社会機能など多くの項目において，DUPが長いほど転帰が不良である[1]。15年あるいは20年後の転帰が不良との報告もある[2]。すなわちDUPの長さは治療反応性の不良と関連し，その効果は長期間持続する可能性がある。またDUPが長いと，寛解に至るまでより長期間を要し，6ヵ月後～5年後において寛解している率が低い[1]。さらに，DUPが長いと再発しやすいという報告[3,4]もある。結果は一致しないが，DUPが長いと認知機能が不良となることも報告されている[2]。

2．DUPと脳構造変化

磁気共鳴画像(magnetic resonance imaging；MRI)などによる脳形態とDUPとの関連が検討されている。これまでの報告のうち，3つのMRI研究[5-7]は，いずれも左の側頭葉，特に上側頭回の体積減少との関連を示している。上側頭回においては，後述のように，初回エピソー

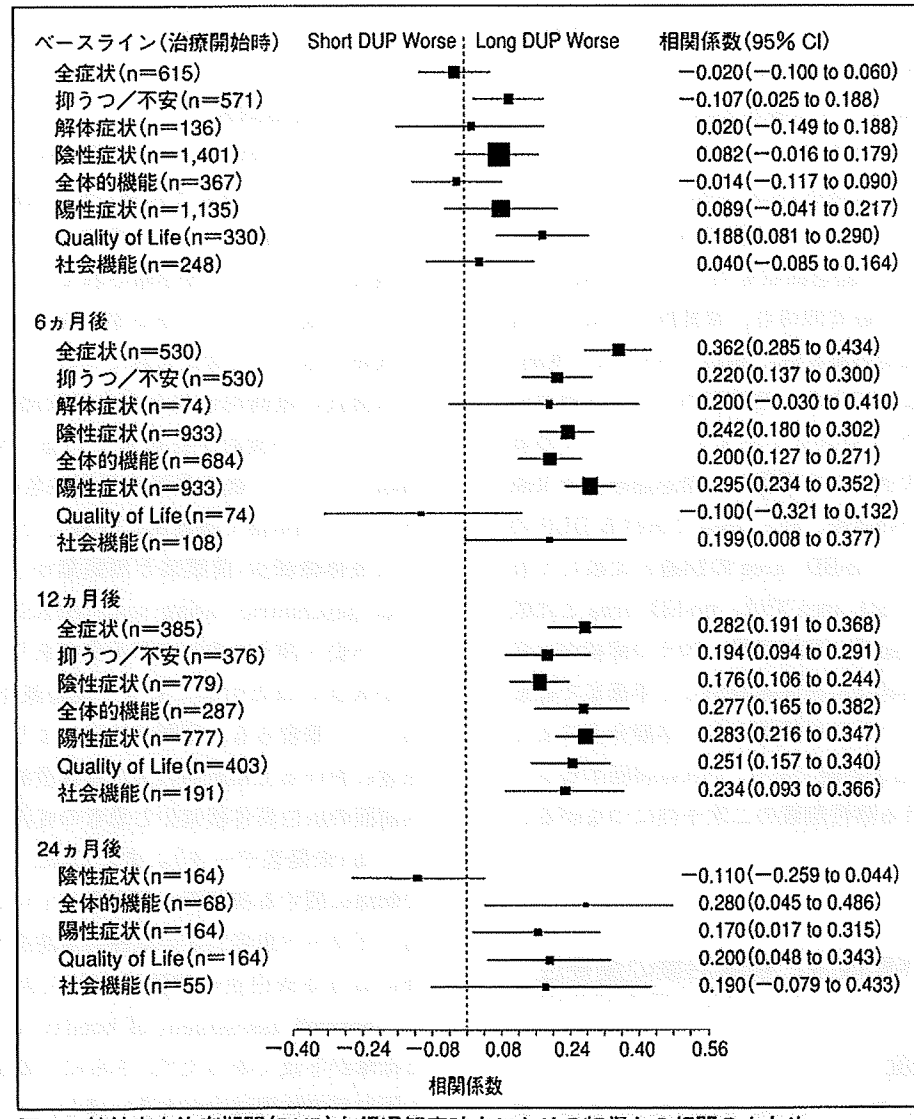

図1．精神病未治療期間(DUP)と経過観察時点における転帰との相関のまとめ
CIは信頼区間，方形の大きさは利用可能なおおよそのデータ数を示す。
(文献1)より引用)

ドおよび前駆期における比較的顕著な進行性体積減少が報告されており，それが転帰に影響する神経生物学的要因の1つである可能性がある。

3．早期介入によるDUPの短縮

Marshallら[11]によるメタ解析に含まれた26の研究におけるDUPの平均値は124週であり，わが国においてもほぼ同様の1～2年と考えられ[8]，決して短いとはいえない。上述のDUPと臨床的転帰との関連から，DUPを短縮することは，初回エピソードからの回復を容易にし，治療反応性を保持し，長期予後の改善に寄与することが示唆される。早期介入によるDUP短縮の効果を，実験的に検証した北欧のTreatment and Intervention in Psychosis(TIPS)studyによる報告を以下に紹介する。

Melleら[9]は，1997～2001年の4年間に，包括的早期発見システムを導入した地区(ED area)と導入しなかった地区(no-ED area)における初発精神病231名について，DUPの調査と2年間の経過観察を行った。包括的早期発見システムとは，①教育関係者，家庭医，若者への啓発活動による早期発見の重要性の周知，②テレビ，新聞，ダイレクトメールなどによる，精神疾患に対する教育的プログラムおよびアンチスティグマキャンペーンの実施，③早期発見臨床チームを設置し，緊急連絡先を公開から成っていた。その結果，ED areaにおけるDUPの中央値は5週であり，no-ED areaの16週と比較して有意に短縮した。またED areaでは，no-ED areaと比較して，2年後の陰性症状，認知症状，抑うつ症状が有意に低く，特に陰性症状は治療開始時から2年後まで軽度のまま維持された。これらの結果から，早期介入によりDUPを短縮することが可能であり，それは初回エピソード統合失調症における陰性徴候の二次予防につながることが示唆される。

2 治療臨界期仮説と初期治療の重要性

1．治療臨界期仮説

治療臨界期仮説(critical period hypothesis)とは，統合失調症の初回エピソードに続く5年ほどの期間は，脆弱性が高く，長期予後に大きな影響を与える「臨界期」と考えられ，より重点的に介入すべきであるというものである[10]。臨界期にはDUPも含まれる。この仮説は，以下のような臨床的観察を根拠としている[10]。

- 多くの症例で，臨床症状や社会的機能などの悪化は発症早期に生じ，発症後2～5年の間に安定化する(plateau effect)。言い換えれば，発症後2年程度の間に達した障害の水準が，長期の障害の水準を強く予測する。
- 再発は最初の2年間に高率に起こり，約8割の患者が5年以内に再発を経験する。
- 本人や家族への心理社会的影響は発症早期に生じる。
- 自殺リスクは発症後2～3年以内が高い。

2．進行性脳病態

これまでの縦断的MRI研究から，統合失調症では前頭葉や側頭葉皮質などに進行性の脳体積減少が認められ，それは初回エピソードを中心とした発症早期に，より顕著に生じることが示唆されている。このような脳構造変化の成因は不明であるが，なんらかの進行性脳病態を反映するものと考えられている。

脳構造の縦断的変化と臨床的転帰との関連についても，いくつか検討が行われている。Nakamuraら[11]は，初回エピソード統合失調症患者29名のMRIを，ベースラインと1.5年後で縦断的に比較した。1.5年間における灰白質体積減少(前頭葉と側頭葉が主体)が大きいほどbrief psychiatric rating scale(BPRS)の総得点，思考障害，不安－抑うつの改善が不良であり，また側脳室の拡大が大きいほど引きこもり－運動減退の改善が不良であった。筆者らも，縦断的検討により，初回エピソード患者における上側頭回の灰白質体積減少と妄想，前頭葉内側面の灰白質体積減少と思考の貧困との関連を見出している(未発表データ)。またCahnら[12][13]は，より長期の転帰に関する興味深い報告をしている。すなわち，初回エピソード患者34名の縦断的追跡を行い，最初の1年間における灰白質の体積減少が大きいほど，2年後のCamberwell assessment of need(CAN)によって評価した転帰が不良であった[12]。さらに，最初の1年間における灰白質の体積減少が大きいほど，5年後の陽性症状および陰性症状が強く，grobal assessment of functioning(GAF)得点が低値で，独立した生活を営んでいる場合

が少なかった[13]。これらの結果は，初期の進行性変化が長期予後を決定する要因であることを示唆しており，治療臨界期仮説を支持するものといえよう。

ところで，進行性の脳形態変化は，前駆期においてすでに生じていると考えることができる。Kasai ら[14]によると，初回エピソード患者では上側頭回の一部である左Heschl 回において4.6%/年，左側頭平面において4.8%/年という，顕著な灰白質体積の減少が生じる。最近のTakahashi ら[15]による検討では，精神病の発症前後で，左側頭平面では5.2%/年，上側頭溝に接する左上側頭回後方部では4.8%/年という，初回エピソードに匹敵する灰白質体積減少が認められている。このような前駆期における変化は，上側頭回だけでなく，前頭前野などより広範囲な領域でも報告されている[16]。

3．抗精神病薬による神経保護作用と予後

上記のような進行性脳病態の観点からは，抗精神病薬による脳体積への影響を検討したLieberman ら[17]の報告が興味深い。すなわち，初回エピソード統合失調症患者を2年間追跡すると，haloperidol 投与群では早期から脳灰白質体積が減少したのに対し，神経保護作用のあるolanzapine を投与した群では健常対照群と変わらなかった。神経保護作用をもつ薬物療法が，進行性脳病態の抑制と予後の改善に寄与できるかは，重要な検討課題である。

また，長期予後改善のためには，初回エピソード寛解後の再発防止が重要で，そのためにはまずアドヒアランスを保つことが肝要である。Nasrallah[18]は，統合失調症の維持療法における持効性注射剤の有用性を認め，脳組織の再生の観点からも，神経保護作用を有する非定型抗精神病薬の持効性注射剤が広く用いられるに値すると説いている。

3 前駆期における介入

1．前駆期介入の意義と問題点

初回治療に至った統合失調症患者の病歴を後方視的にみると，短からぬDUP と，さらにさかのぼって平均数年に及ぶ前駆期が認められることが多い。前駆期にはすでに社会機能などの低下が生じている。前駆期の始まりから治療開始までの期間を，疾病未治療期間(duration of untreated illness；DUI)と呼ぶが，DUP よりむしろDUI のほうが，8年後の生活機能水準の予測因子であったという報告[19]もある。進行性脳病態が前駆期から生じていることを示す研究報告からも，前駆期の適切な治療が長期予後の改善に結びつくと期待できるかもしれない。また，当然ながら，顕在発症予防の可能性も期待される。

しかし，実際に精神病症状が顕在化する以前に介入することにはさまざまな困難がある。前方視的に前駆期の特異的診断はまだできないので，特定の徴候を有する者を精神病発症リスクの高い状態(at risk mental state；ARMS)[20]，すなわち前駆期の疑いとして，操作的に診断して介入を行う方法が一般的となっている。ところが，ARMS と診断されても，その後の1年間に精神病に移行する率は20～40%程度と報告されており，かなりの率で偽陽性(前駆症状類似の症状を示すが，実際には精神病を発症することのない一群)が存在すると考えられる。このため，ARMS に対する介入においては，患者が現在感じている苦悩への対応が優先される。顕在発症予防を目的とした治療的介入研究を行う際には，偽陽性の存在のために，介入すべき対象は不明確となり，また介入の効果判定も困難となる[15]。

2．これまでの介入研究

上記のような問題はあるものの，発症予防を視野に入れた，ARMS に対する治療的介入研究がいくつか報告されている[16]。低用量のrisperidone と認知行動療法(cognitive behavioral therapy；CBT)の併用による6ヵ月間の介入では，精神病移行率の有意な低下が観察されたが，介入終了の6ヵ月後には有意差は消失した[21]。しかしrisperidone に対するアドヒアランス良好群では，効果が長期間維持されたという。またolanzapine による12ヵ月間の介入により，精神病移行率の低下傾向と陽性前駆症状の有意な改善が認められたことが報告されている[22]。CBT 単独による精神病移行率の有意な低下も報告されている[23]。

これらの研究の症例数は十分ではなく，決定的な結果とはいえない。治療的介入により，精神病の顕在発症を

遅延させうることは示唆されているが，発症予防効果に関しては今のところ不明である。介入しながらも発症に至った場合は，強制入院などを要さず，速やかかつ穏やかに治療を開始できることが指摘されており[23]，短期の転帰は良好といえるが，長期予後への効果については不明である。

おわりに

初回エピソードとそれに引き続く数年間は，長期予後に大きな影響を及ぼす治療臨界期と考えられ，この時期に重点的に医療資源を注ぎ込んで，治療の充実を図ることが求められる。DUPを短縮するとともに，効果的な薬物療法および心理社会的治療により早期寛解を目指すことが目標となる。また，寛解後の再発と難治化を防止することも重要である。常に精神病体験による悪影響を最小限にし，社会・職業的機能を最大限に保つことに努めるべきである。前駆期における積極的介入については，実践しながら，エビデンスを集積していくことが重要であろう。

脳画像診断による研究結果も早期介入の重要性を支持している。今後は，発症早期に生じることが示唆される進行性脳病態の解明が重要である。早期治療の充実により進行性変化を防止できる可能性があり，それを長期予後改善のための治療標的として検討を進めることが有益と思われる。

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Insular cortex gray matter changes in individuals at ultra-high-risk of developing psychosis

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ABSTRACT

Morphologic abnormalities of the insular cortex have been described in psychotic disorders such as schizophrenia, but it remains unclear whether these changes predate the onset of psychosis or develop progressively over the course of illness. In this study, we used magnetic resonance imaging to investigate the gray matter volume of the long and short insular cortices in 97 neuroleptic-naïve individuals at ultra-high-risk (UHR) for developing psychosis [of whom 31 (32%) later developed psychosis (UHR-P) and 66 (68%) did not (UHR-NP)] and 55 age- and gender-matched healthy comparisons. We also conducted a longitudinal comparison of the insular cortex gray matter changes in 31 UHR individuals (20 UHR-NP and 11 UHR-P) and 20 controls for whom follow-up MRI data between 1 and 4 years later were available. In the cross-sectional comparison, the UHR-P subjects had a significantly smaller insular cortex compared with the UHR-NP subjects bilaterally and with the controls on the right hemisphere, especially for the short insular region. More severe negative symptoms in UHR-P subjects at baseline were associated with smaller volumes of the right long insular cortex. In the longitudinal comparison, the UHR-P subjects showed greater gray matter reduction of insular cortex bilaterally (−5.0%/year) compared with controls (−0.4%/year) or UHR-NP subjects (−0.6%/year). Our findings suggest that insular cortex gray matter abnormalities in psychotic disorders may reflect pre-existing vulnerability, but that there are also active progressive changes of the insular cortex during the transition period into psychosis. Whether these longitudinal changes are features of the disorder or related to treatment with antipsychotic medication remains to be determined.

1. Introduction

Convergent evidence suggests that schizophrenia and related psychoses are associated with subtle but widespread morphologic brain changes, predominantly in the fronto-temporolimbic–paralimbic regions (Shenton et al., 2001). These changes are already present in first-episode psychosis patients (Vita et al., 2006), but several longitudinal magnetic resonance imaging (MRI) studies in first-episode schizophrenia have demonstrated progressive brain changes in the years following illness onset (Gur et al., 1998; Ho et al., 2003; Kasai et al., 2003a,b; Nakamura et al., 2007; Sun et al., in press). These observations suggest that brain morphologic abnormalities in

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psychotic disorders might reflect a combination of pre-existing vulnerability and changes associated with the first expression of psychotic symptoms (Pantelis et al., 2005, 2007).

Recent MRI studies of high-risk populations around the period of transition to psychosis (Borgwardt et al., 2007, 2008; Job et al., 2003, 2005; Meisenzahl et al., 2008; Pantelis et al., 2003) have further supported this multiple-hit model of psychosis. The few cross-sectional voxel-based morphometric (VBM) findings in these patients demonstrated that some of the brain morphologic changes associated with psychosis, such as gray matter reduction in right superior temporal gyrus and right insular cortex, predate the onset of frank symptoms (Borgwardt et al., 2007; Pantelis et al., 2003). Longitudinal VBM studies in genetic (Job et al., 2005) or clinical (Borgwardt et al., 2008; Pantelis et al., 2003) high-risk subjects reported progressive gray matter reductions in several brain regions including orbitofrontal and fronto-temporal areas as well as bilateral cingulate cortex over the transition phase, although these studies have potential methodological problems of brain registration (Crum et al., 2003; Giuliani et al., 2005). Our recent study based on cortical pattern matching (Sun et al., 2009), which allows more sensitive analysis of the lateral cortical surface than does VBM, demonstrated increased brain surface contraction in prefrontal regions during illness transition. However, this approach cannot examine the cortical regions in deep sulci such as the insular cortex.

Morphologic abnormalities of the insular cortex, which plays crucial roles in emotional and various cognitive functions as a component of the limbic integration cortex (Augustine, 1996), have been repeatedly described in schizophrenia (Crespo-Facorro et al., 2000; Kasai et al., 2003c; Kim et al., 2003; Makris et al., 2006; Saze et al., 2007; Takahashi et al., 2004, 2005). Although the short and long subregions of the insular cortex are functionally distinct (Augustine, 1996; Türe et al., 1999), it is unclear whether they are differentially affected in the disorder. Gray matter reduction or dysfunction of the insular cortex has been implicated in manifesting psychotic symptoms (Crespo-Facorro et al., 2000; Shapleske et al., 2002; Shergill et al., 2000), cognitive impairments (Crespo-Facorro et al., 2001a,b,c; Curtis et al., 1998), and as a potential marker of later transition to psychosis (Borgwardt et al., 2007; Pantelis et al., 2003). Furthermore, while it is unclear whether there is progressive atrophy of the insular cortex around the time of onset of psychosis, the inverse correlation between the insular cortex gray matter volume and duration of prodromal phase in first-episode psychosis is suggestive (Lappin et al., 2007). Current evidence thus suggests that insular cortex abnormalities in psychotic disorders may reflect both vulnerability to psychosis and ongoing progressive pathology related to emerging florid symptoms.

In this study, we conducted volumetric ROI analysis of the insular cortex subregions in both cross-sectional and longitudinal MRI data from individuals at ultra-high risk (UHR) for psychosis (Yung et al., 2003, 2004b). Based on previous studies, we predicted that UHR individuals who later developed psychosis (UHR-P) would have smaller right insular cortex compared with those did not develop psychosis (UHR-NP) or control subjects at baseline. A further prediction was that there would also be progressive gray matter reduction of the insular cortex in UHR-P individuals during the transition to psychosis.

2. Methods

2.1. Subjects

We enrolled 97 neuroleptic-naïve UHR individuals and 55 healthy comparisons for the cross-sectional comparison (Table 1). All participants were screened for co-morbid medical and psychiatric conditions by clinical assessment, physical and neurological examination. Exclusion criteria were a history of significant head injury, seizures, neurological diseases, impaired thyroid function, diabetes, corticosteroid use, or DSM-IV criteria of alcohol or substance abuse or dependence (American Psychiatric Association, 1994).

The UHR subjects were recruited from admissions to the Personal Assessment and Crisis Evaluation (PACE) Clinic, which was established to identify young people at clinical risk for developing a first psychotic episode within a short follow-up period (McGorry et al., 2002; Yung et al., 2004b). The UHR

Table 1
Demographic and clinical data of healthy controls and ultra-high risk (UHR) individuals.

	Cross-sectional analysis				Longitudinal analysis			
	Controls ($n=55$)	UHR-NP ($n=66$)	UHR-P ($n=31$)	p	Controls ($n=20$)	UHR-NP ($n=20$)	UHR-P ($n=11$)	p
Male/female	36/19	39/27	20/11	0.75	12/8	11/9	6/5	0.94
Handedness (right/mixed/left)	51/1/2	54/2/9	28/0/3	0.32	20/0/0	15/1/4	9/0/2	0.19
Premorbid IQ[a]	101.6 (10.2)	95.9 (14.4)	94.0 (12.0)	0.02	102.7 (9.6)	93.4 (14.9)	92.1 (11.3)	0.04
Age at baseline scan (years)	20.8 (3.6)	20.2 (3.3)	19.1 (3.6)	0.08	21.6 (4.7)	20.3 (4.3)	19.5 (5.3)	0.45
Age at second scan (years)	–	–	–	–	23.7 (5.0)	21.7 (4.3)	20.7 (5.4)	0.22
Days between scans	–	–	–	–	774 (291)	531 (306)	462 (183)	<0.01
Age of onset (year)	–	–	19.6 (3.6)	–	–	–	20.1 (5.2)	–
Days between baseline scan and onset	–	–	199 (199)	–	–	–	216 (147)	–
Days between onset and second scan	–	–	–	–	–	–	246 (142)	–
BPRS score at intake	–	17.9 (7.1)	18.9 (7.2)	0.55	–	17.7 (8.4)	19.5 (9.4)	0.59
SANS score at intake	–	19.7 (14.2)	29.0 (15.7)	<0.01	–	18.2 (10.9)	29.0 (16.8)	<0.01
Intracranial volume (cm^3)[b]	1454.3 (152.6)	1416.3 (145.9)	1470.1 (128.6)	0.16	1416.9 (148.5)	1428.4 (160.7)	1477.5 (139.4)	0.47

Data are presented as mean (SD) otherwise stated.
BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; UHR-NP, ultra-high risk nonpsychotic; UHR-P, ultra-high risk psychotic.
[a] National Adult Reading Test (NART) data were not available for 19 subjects.
[b] Age was used as a covariate for ANCOVA analysis.

identification criteria and the rationale for these criteria have been fully described elsewhere (Yung et al., 2003, 2004b, 2005). All UHR subjects were aged 14–30 years, had not experienced a previous psychotic episode, had *never* received neuroleptic medication (incl. antipsychotics, antidepressants, mood stabilizers, or benzodiazepines), and were not intellectually disabled [IQ >70, assessed by the National Adult Reading Test (Nelson and O'Connell, 1978)]. At intake, the UHR subjects were assessed with the Brief Psychiatric Rating Scale (BPRS) (Rhoades and Overall, 1988), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), and the Comprehensive Assessment of At Risk Mental States (Yung et al., 2004a). After baseline MRI, they were monitored regularly for the onset of full threshold psychosis and were then divided into subgroups based on operationalized criteria for psychosis onset (Yung et al., 2004b) and Structural Clinical Interview for DSM-IV diagnoses (First et al., 1997). Individuals were included in the study if they had been followed up for at least one year, unless onset of psychosis occurred earlier (mean = 1.1 years, maximum = 3.7 years). Thirty-one of the UHR subjects developed a psychotic illness (UHR-P) during follow-up; 19 developed schizophrenia spectrum (17 schizophrenia and 2 schizoaffective disorder), 10 an affective psychosis (5 major depressive disorder with psychotic features and 5 bipolar disorder with psychotic features), and 2 other psychoses (1 psychosis not otherwise specified and 1 brief psychosis). Of the 66 UHR subjects who did not develop psychosis (UHR-NP), 25 presented with a nonpsychotic Axis I disorder at follow-up; 12 had a depressive disorder (4 with major depressive disorder, 8 with dysthymia), 9 had an anxiety disorder, 1 had an adjustment disorder, 1 had an eating disorder, and 2 had a substance-induced mood disorder. After the baseline scan, 16 subjects (5 with and 11 without later transition) started low-dose risperidone therapy (mean dose = 1.3 mg/day) and cognitive behavior therapy as part of an intervention trial (McGorry et al., 2002). Most of the remaining UHR participants received case management and supportive therapy. Most UHR-P subjects received atypical antipsychotics after onset, but complete information on medications was not available. The healthy volunteers were recruited from similar socio-demographic areas as the patients by approaching ancillary hospital staff and through advertisements. Comparison subjects with a personal or family history of psychiatric illness were excluded.

Follow-up MRI data were available for 31 (32%, 20 UHR-NP and 11 UHR-P) of 97 UHR subjects and 20 (36%) of 55 controls. The characteristics of this sub-sample are largely comparable with those of the whole sample in this study (Table 1). Thirty-one and 16 UHR subjects overlapped with our previous cortical pattern matching (Sun et al., 2009) and VBM (Pantelis et al., 2003) studies, respectively. This study was approved by local research and ethics committees, and written informed consent was obtained from the participants or their parents/guardians where appropriate.

2.2. MRI procedures

All subjects were scanned on a Signa 1.5-T scanner (General Electric Medical Systems, Milwaukee, Wisconsin). A three-dimensional volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous 1.5-mm coronal slices. Parameters were: echo time, 3.3 ms; repetition time, 14.3 ms; flip angle, 30°; matrix size, 256×256; field of view, 24×24-cm matrix; and voxel dimensions, 0.938×0.938×1.5 mm. For longitudinal comparison, we

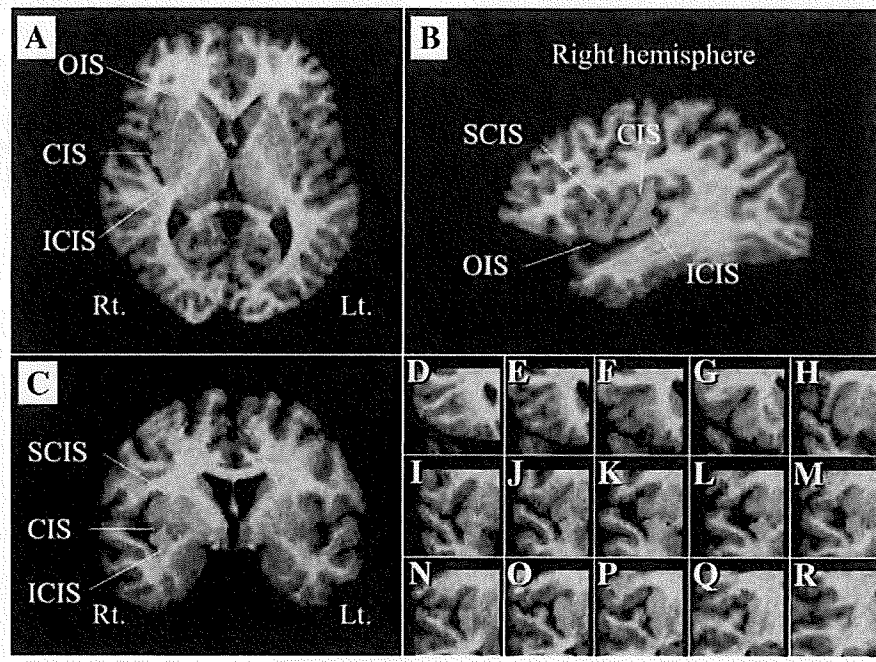

Fig. 1. Axial (A), sagittal (B), and coronal (C) views of the short (blue) and long (red) insular cortices manually traced in this study. Sample coronal images D through R move progressively in a rostral to caudal direction. Abbreviations: CIS = central insular sulcus; ICIS = inferior circular insular sulcus; OIS = orbitoinsular sulcus; SCIS = superior circular insular sulcus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rescanned a subset of individuals for whom follow-up scanning was possible on the same scanner with the same protocol. The scanner was calibrated fortnightly with the same phantom to ensure stability of measurements.

The image data were coded randomly and analyzed with the Dr View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images, with a 0.938-mm thickness, perpendicular to the AC-PC line. The whole cerebrum was manually separated from the brainstem and cerebellum. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were used to semi-automatically segment the voxels into gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Eritaia et al., 2000); the groups did not differ significantly in their ICVs (Table 1).

2.3. Insular cortex measurements

Based on the segmented gray matter images, the insular cortex was traced on 0.938-mm consecutive coronal slices as described elsewhere (Takahashi et al., 2005). Briefly, the most rostral coronal slice containing the insular cortex and the coronal plane containing the fusion of the superior and inferior circular insular sulci were chosen as anterior and posterior boundaries, respectively. On each coronal slice, the insular cortex was bounded superiorly by the superior circular insular sulcus and inferiorly by the inferior circular insular sulcus or the orbitoinsular sulcus. The insular cortex was then divided into the short and long insular cortices by the central insular sulcus, which was readily identified using both coronal and sagittal views (Fig. 1).

All volumetric data reported here were measured by one rater (TT), who was blinded to subjects' identities or time of scan. The volumes of the short and long insular cortices in a subset of 10 randomly selected brains were measured independently by two raters (TT and RT), and each volume was then remeasured after at least 4 weeks by the first-rater; intra-/inter-rater intraclass correlation coefficients of the short and long insular cortex measurements were 0.96/0.98 and 0.98/0.95, respectively.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test.

The absolute insular cortex volume at baseline was assessed using a repeated measures analysis of covariance (ANCOVA) with age, gender, and ICV as covariates, with group (controls, UHR-NP, and UHR-P) as a between-subject factor, and side and subregion (short, long) as within-subject variables. Based on a prominent subregional effect in this analysis [F (1, 149) = 1580.57, $p<0.001$] and possible subregional specificity of the insular cortex abnormality in the neurobiology of psychosis (Makris et al., 2006), the short and long insular cortices were also separately analyzed.

The longitudinal volume change of the insular cortex was analyzed using the percent volume change [100 × (absolute volume at second scan − absolute volume at baseline) / absolute volume at baseline] as the dependent variable. A repeated measure ANCOVA with inter-scan interval (year), age at first scan, gender, and ICV as covariates, diagnosis as a between-subject factor, and side and subregion as within-subject variables was performed. The percent volume changes for insular cortex subregions were normally distributed (Kolmogorov–Smirnov test). Post-hoc Scheffé's tests were used to follow up the significant main effects or interactions yielded by these analyses. The statistical conclusions reported here remained the same when we investigated the gray matter loss over time by using ANCOVA with side, subregion, and time of scan (baseline, second scan) as within-subject variables or when we used annual percent volume change [percent volume change/inter-scan interval (year)] (Table 2) as the dependent variable.

The association between the volumes of the long and short insular cortex at baseline and the SANS and BPRS intake scores as well as premorbid IQ was examined using Pearson's partial correlation coefficients controlling for ICV. The SANS/BPRS scores and premorbid IQ were normally distributed (Kolmogorov–Smirnov test). The association of premorbid IQ to percent volume changes for insular cortex subregions was also examined using ICV, age, and inter-scan interval as controlling factors. Statistical significance was defined as $p<0.05$ (two-tailed).

Table 2
Absolute volume and volume change over time of the insular cortex.

Brain region	Baseline volume (mm^3)			Analysis of covariance[a]						% change per year[b]		
	Controls ($n=55$)	UHR-NP ($n=66$)	UHR-P ($n=31$)	Group		Side		Group × side		Controls ($n=20$)	UHR-NP ($n=20$)	UHR-P ($n=11$)
				F	p	F	p	F	p			
Short insular cortex				8.58	<0.001	36.41	<0.001	4.05	0.019			
Left	5449 (898)	5546 (812)	5269 (884)							−0.1 (3.1)	−0.7 (3.0)	−5.5 (3.3)
Right	5326 (711)	5277 (706)	4782 (684)[c]							−0.8 (4.1)	−0.6 (4.0)	−4.5 (3.4)
Long insular cortex[d]				4.36	0.014	10.17	0.002	0.83	0.435			
Left[e]	3208 (629)	3195 (568)	3137 (442)							0.0 (3.9)	−0.6 (3.4)	−5.7 (3.7)
Right	3111 (465)	3117 (573)	2931 (437)							−0.4 (2.9)	−0.3 (3.9)	−4.6 (4.9)

Data are presented as mean (SD). UHR-NP, ultra-high risk nonpsychotic; UHR-P, ultra-high risk psychotic.
[a]Short and long insular cortices were separately analyzed with age, gender, and intracranial volume as covariates, group as between-subject factor, and side as a within-subject variable. $df=2, 146$ for the effect of group, 1, 149 for the effect of side, and 2, 149 for group-by-side interaction.
[b]Calculated as follows: (100 × [absolute volume at second scan − absolute volume at baseline] / absolute volume at baseline) / inter-scan interval (year).
The statistical analyses for longitudinal volume changes were based on the percent volume changes covarying for inter-scan interval (see text).
Post-hoc tests showed: [c]$p<0.001$, smaller than in controls and UHR-NP; [d]no group differences; and [e]$p=0.001$, larger than on right side.

3. Results

3.1. Sample characteristics

Groups were matched for age, gender, handedness, but the control subjects had a higher premorbid IQ than UHR-P individuals (Table 1). Baseline SANS score, but not BPRS score, was higher in UHR-P subjects. In the longitudinal comparison, the interval between scans was significantly longer for the controls compared with both UHR groups [F (2, 48) = 5.83, p = 0.005].

3.2. Cross-sectional comparison at baseline

Table 2 summarizes the insular cortex measurements. ANCOVA revealed significant main effects for group [F (2, 146) = 10.27, p<0.001], side [F (1, 149) = 65.87, p<0.001], and subregion [F (1, 149) = 1580.57, p<0.001], and group-by-side [F (2, 149) = 6.12, p = 0.003] and side-by-subregion [F (1, 149) = 5.30, p = 0.023] interactions. Post-hoc analyses showed that the UHR-P subjects had a smaller insular cortex compared with the UHR-NP subjects bilaterally (left, p = 0.032; right, p<0.001) and with the controls on the right hemisphere (p<0.001), but there was no difference between the UHR-NP and control subjects. The short insular cortex had a leftward asymmetry for all diagnostic groups (p<0.001). There was no significant group-by-subregion interaction in the ANCOVA analysis [F (2, 149) = 1.97, p = 0.143], implying that the group difference in the insular cortex volume was not highly specific for one subregion. When the short and long insular cortices were analyzed separately, however, a significant volume reduction in the UHR-P subjects was demonstrated only for the short insular cortex on the right hemisphere (Table 2). These results did not change even when we excluded subjects with records for significant quantities of cannabis use (3 UHR-P, 6 UHR-NP, and 2 control subjects) [group-by-side interaction for short insula, F (2, 138) = 3.97, p = 0.021, UHR-P<UHR-NP, controls (post-hoc test, p<0.001); group effect for long insula, F (2, 135) = 6.37, p = 0.002, no group differences (post-hoc test)].

3.3. Longitudinal comparison

ANCOVA of the percent volume change revealed a significant main effect for group [F (2, 44) = 6.93, p = 0.002], but there was no significant effect of subregion or side. Post-hoc analyses demonstrated that the UHR-P subjects [mean = −5.6%; effect size relative to controls, Cohen's d = 1.3 (left), 0.7 (right)] had a greater gray matter reduction of the insular cortex compared with controls (mean = −0.4%) (p = 0.008) or UHR-NP subjects [mean = −0.5%; effect size relative to controls, Cohen's d = 0.1 (left), −0.1 (right)] (p = 0.010), while there was no difference between the controls and UHR-NP subjects (p = 0.995) (Fig. 2). Exclusion of cannabis users (1 UHR-P and 2 UHR-NP subjects) did not change the findings [effect of group, F (2, 41) = 5.78, p = 0.006, UHR-P greater gray matter loss than UHR-NP (p = 0.015) and control subjects (p = 0.022)].

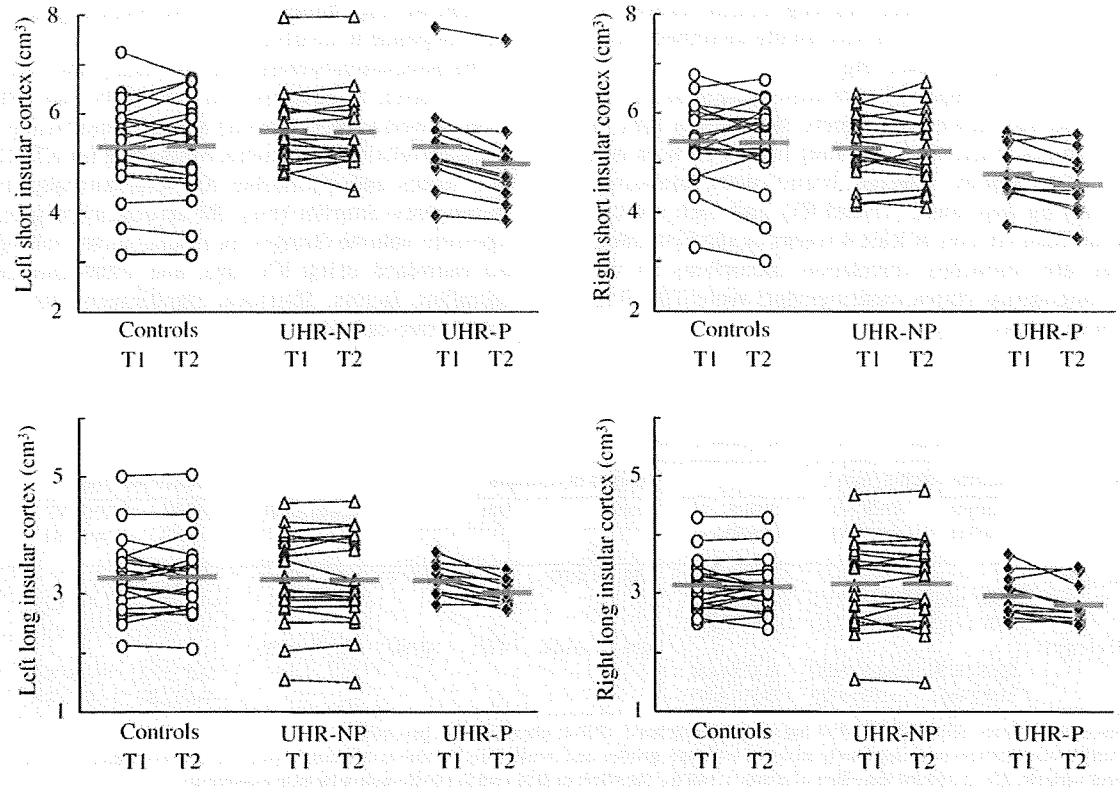

Fig. 2. Scatterplots of absolute volumes of short and long insular cortices in healthy controls, ultra-high-risk nonpsychotic (UHR-NP) subjects, and ultra-high-risk psychotic (UHR-P) subjects. Values of baseline (T1) and follow-up scan (T2) in each subject are connected with a straight line. Horizontal bars indicate means of each group.

3.4. Correlational analysis

There was a negative correlation between the right long insular cortex volume at baseline and the intake SANS score for the UHR-P ($r=-0.483$, $p=0.007$) but not for UHR-NP ($r=-0.166$, $p=0.189$) subjects, although these correlations were not significantly different ($p=0.114$, Fisher's Z transformation). The BPRS score did not significantly correlate with insular cortex volume for either UHR group ($r=-0.321$ to 0.098, $p=0.084$ to 0.733). Premorbid IQ did not correlate with baseline volume ($r=-0.123$ to 0.306, $p=0.137$ to 0.987) or volume reduction over time ($r=-0.477$ to 0.347, $p=0.117$ to 0.833) of the insular cortex in either group.

4. Discussion

To our knowledge, this is the first ROI-based MRI study to report gray matter changes of the insular subregions in UHR individuals in both cross-sectional and longitudinal designs. In the cross-sectional baseline comparison, the neuroleptic-naïve UHR subjects who later developed psychosis (UHR-P) had a smaller insular cortex volume compared with those who did not (UHR-NP) or healthy controls. This was particularly prominent for the right hemisphere. This baseline group difference did not show prominent subregional effect, but tended to be more evident for the short insula. In the longitudinal comparison, the UHR-P subjects showed significantly greater gray matter loss in bilateral insular cortex than UHR-NP subjects or healthy comparisons. These findings indicate that there are insular cortex abnormalities prior to the onset of psychotic disorders which are not due to medication, and that these progress across the transition to illness.

Our cross-sectional findings are consistent with previous VBM studies (Borgwardt et al., 2007; Pantelis et al., 2003), which demonstrated that UHR-P subjects had less right insular gray matter at baseline than UHR-NP. Recent cross-sectional VBM analysis by Meisenzahl et al. (2008) also found right-sided gray matter reduction of the insular cortex in their high-risk cohort, recruited by means of a combination of 'basic symptoms' (Klosterkotter et al., 2001) and our UHR criteria, compared to healthy controls, although this analysis did not differentiate the subjects with and without later transition. Genetically predisposed subjects do not seem to show these abnormalities (Job et al., 2003), but it is possible that this is due to the low transition rate (10–15%) (Johnstone et al., 2000). The current findings of the UHR-NP subjects are generally in line with our previous ROI-based MRI study (Takahashi et al., 2005) that reported preserved insular cortex volume in subjects with schizotypal personality disorder (SPD); these SPD subjects, who did not develop psychosis during follow-up period (mean = 2.0 years), are considered to be comparable with our UHR-NP subjects, as the SPD subjects with decreased functioning also fulfill the UHR criteria. Thus, the present and these previous observations suggest that the insular cortex volume in the prodromal phase, especially on the right, could be one of the neurobiological predictors of future transition to psychosis, which may contribute to specific and targeted preventive strategies (Johnstone et al., 2005; McGorry et al., 2006).

The anterior (short) and posterior (long) subregions of the insular cortex have been reported to be different both functionally and in terms of their anatomical connections (Augustine, 1996). The short insula has extensive connections with the frontal lobe and is involved in emotional and language-related functions, whereas the long insula, which includes somatosensory and auditory processing areas, connects with the parietal and temporal lobes. Regarding the topographical specificity of the insular cortex, as in our cross-sectional finding of UHR-P subjects, previous MRI studies in schizophrenia indicated a global volume reduction (Kasai et al., 2003c; Saze et al., 2007; Takahashi et al., 2005) or a reduction predominantly in anterior portion (Makris et al., 2006), supporting the notion that neuroanatomical alterations associated with an increased vulnerability to psychosis are qualitatively similar to those in schizophrenia (Borgwardt et al., 2007).

The current longitudinal comparison indicated further progressive gray matter reduction of the insular cortex bilaterally during the transition psychosis. The nature of active brain changes in the course of psychotic disorders has been largely unknown, whereas the naturalistic observations of schizophrenia have suggested that the neurobiological deterioration commences 2 to 3 years before onset (McGlashan, 1999). The findings of the present study provide evidence that the rate of insular cortex reduction in the UHR-P subjects (−5.0%/year) is greater than that seen in patients with first-episode psychosis (−2.2%/year) or chronic schizophrenia (−0.7%/year) (Takahashi et al., 2009). The fact that we didn't find these changes in our previous VBM study (Pantelis et al., 2003) may be partly explained by the different resolutions of the images, as well as the obvious methodological differences (i.e., VBM versus ROI approach; Giuliani et al., 2005). The present and our earlier studies thus suggest that a regional progressive pathological process in the insular cortex precedes the first expression of florid psychosis, and may be particularly severe during the transition period.

The intake SANS score of the UHR-P subjects was negatively correlated with right long insular cortex volume, partly consistent with the role of the insular cortex abnormalities in negative symptomatology (Sigmundsson et al., 2001; Takahashi et al., 2004) or emotional deficit (Crespo-Facorro et al., 2001a) in schizophrenia. As for the topographical specificity (Augustine, 1996; Türe et al., 1999), this correlation was contrary to prior prediction, as the short insular cortex, but not the long insular cortex, is critically involved in emotion and has close connections with the prefrontal brain areas, which are likely to be relevant to both negative and positive symptoms in clinical high-risk subjects (Meisenzahl et al., 2008). Nevertheless, our findings suggest the association between the prodromal symptomatology and brain morphology especially for high-risk subjects with later transition.

The exact neurobiological basis for insular cortex gray matter changes in psychotic disorders is unknown. A neuronal migration disturbance during early neurodevelopment, as suggested by poorly developed layers II and III of the dorsal insular cortex in schizophrenic brains (Jakob and Beckmann, 1986), might be related to smaller insular cortex gray matter volume in the prodromal phase. However, these cytoarchitectonic abnormalities cannot explain the ongoing

gray matter reduction over the transition. This MRI study cannot determine the underlying pathological mechanism, but anomalies of synaptic plasticity and abnormal brain maturation, as well as stress or other environmental factors may be relevant (Pantelis et al., 2005).

A few possible confounding factors in the present study should be taken into account. First, some participants withdrew from their medication or failed to make outpatient consultations during the follow-up so that the sample size for longitudinal comparison was small and their entire clinical data (e.g., cumulative dose of antipsychotics) were not available. It is possible that the longitudinal gray matter changes evident in UHR-P individuals were related to antipsychotic treatment after onset. However, we have previously shown no correlation between insular cortex reduction and antipsychotic dose in a first-episode group (Takahashi et al., 2009), and comparison of UHR-NP subjects in the current study who did ($n=6$) or did not ($n=14$) receive risperidone reveals no significant difference in longitudinal insular changes [$F(1, 15)=2.37$, $p=0.144$]. Furthermore, the effects of medication alone cannot explain the marked volume changes in UHR-P subjects who were treated with low-doses of atypical antipsychotics (Dazzan et al., 2005; Lieberman et al., 2005; Molina et al., 2005), and progressive gray matter reductions are also seen in neuroleptic-naïve genetically high-risk cohorts (Gogtay et al., 2007; Job et al., 2005). Secondly, 11 subjects in this study (3 UHR-P, 6 UHR-NP, and 2 control subjects) used significant quantities of cannabis, which could potentially affect brain morphology (Yücel et al., 2008). However, the level of use reported to result in gray matter changes is far greater and for a much longer duration than that found in these 11 participants. In any case, exclusion of these subjects did not change the findings. The UHR-P subjects had a lower IQ than controls, but premorbid IQ did not significantly correlate with baseline volume or volume reduction over time of the insular cortex in either group. Finally, although most psychotic patients met diagnostic criteria for schizophrenia spectrum disorders, our cohort included a rather diverse population with psychotic symptoms and the findings of the present study could be relevant to psychoses in general. Neurobiological similarities and differences between established schizophrenia and other psychoses such as bipolar disorder remain controversial (Maier et al., 2006; Murray et al., 2004). Although we found no group difference in the insular cortex volume at baseline between the UHR-P subjects who developed schizophrenia spectrum ($n=19$) and who developed affective psychosis ($n=10$) [$F(1, 25)=0.05$, $p=0.826$], further work will be required to clarify the diagnostic specificity of our findings in a larger sample.

In summary, the present study indicates that the insular cortex abnormalities, especially on the right, predate first expression of frank psychosis, possibly reflecting pre-existing vulnerability to psychosis. This finding raises the possibility that the morphology of the insula during the prodromal phase could be a candidate neurobiological predictor of future transition. Our findings also suggest a regional progressive pathological process of bilateral insular cortex during the transition period, providing an impetus for further studies to prevent or ameliorate the active brain changes by early intervention during or before the first episode of psychosis.

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Contributors

Drs. Suzuki, Velakoulis, and Pantelis conceived the idea and methodology of the study. Dr. Takahashi conducted the statistical analyses and wrote the manuscript. Drs. Wood, McGorry, Yung, Phillips and Velakoulis recruited subjects, were involved in clinical and diagnostic assessments and for MRI scanning. Drs. Takahashi and Tanino analyzed magnetic resonance imaging. Ms. Soulsby and Dr. Zhou provided technical support (data processing). All authors contributed in writing of the manuscript and have approved the final manuscript.

Conflict of interest

There are no conflicts of interest for any of the authors.

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The Disrupted-in-Schizophrenia-1 Ser704Cys polymorphism and brain morphology in schizophrenia

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ABSTRACT

The Disrupted-in-Schizophrenia-1 (DISC1) polymorphism is a strong candidate for a schizophrenia-susceptibility gene as it is widely expressed in cortical and limbic regions, but the effect of its genotype variation on brain morphology in schizophrenia is not well known. This study examined the association between the DISC1 Ser704Cys polymorphism and volumetric measurements for a broad range of fronto-parietal, temporal, and limbic–paralimbic regions using magnetic resonance imaging in a Japanese sample of 33 schizophrenia patients and 29 healthy comparison subjects. The Cys carriers had significantly larger volumes of the medial superior frontal gyrus and short insular cortex than the Ser homozygotes only for healthy comparison subjects. The Cys carriers tended to have a smaller supramarginal gyrus than the Ser homozygotes in schizophrenia patients, but not in healthy comparison subjects. The right medial superior frontal gyrus volume was significantly correlated with daily dosage of antipsychotic medication in Ser homozygote schizophrenia patients. These different genotype effects of the DISC1 Ser704Cys polymorphism on the brain morphology in schizophrenia patients and healthy comparison subjects suggest that variation in the DISC1 gene might be, at least partly, involved in the neurobiology of schizophrenia. Our findings also suggest that the DISC1 genotype variation might have some relevance to the medication effect on brain morphology in schizophrenia.

1. Introduction

Schizophrenia is a heterogeneous psychiatric disorder with a multifactorial etiology in which multiple susceptibility genes interact with environmental insults (Sawa and Snyder, 2002; Harrison and Weinberger, 2005). Besides subtle, but widespread, morphologic brain changes and a broad range of cognitive impairments, convergent evidence from neuroimaging studies suggests that a pathological process in schizophrenia predominantly affects the fronto–temporolimbic–paralimbic regions (Shenton et al., 2001; Suzuki et al., 2002). Recent observations further revealed the importance of the parietal regions in the pathophysiology of schizophrenia (Kim et al., 2003; Danckert et al., 2004; Zhou et al., 2007). In addition to gray matter reduction (Kubicki et al., 2002; Buchanan et al., 2004; Zhou et al., 2007), the parietal cortex has been implicated in manifesting psychotic symptoms and cognitive deficits (Kim et al., 2003; Danckert et al., 2004) as a component of an impaired fronto–parietal network (Barash, 2003; Simon et al., 2004) in schizophrenia.

The Disrupted-in-Schizophrenia-1 (DISC1) gene was first identified at the breakpoint of a balanced (1;11)(q42.1;q14.3) translocation segregating with schizophrenia and related psychotic disorders in a large Scottish family (St Clair et al., 1990; Millar et al., 2000). The DISC1 has been a strong candidate for a schizophrenia-susceptibility gene based on subsequent linkage and association studies in independent populations (Harrison and Weinberger, 2005; Ishizuka et al., 2006; Roberts, 2007). The DISC1 is thought to be involved in mechanisms of neurodevelopment and synaptic plasticity (Kamiya et al., 2005; Kirkpatrick et al., 2006; Ozeki et al., 2003; Taya et al., 2007) and is expressed in human brain regions known to be abnormal in schizophrenia such as the frontal and parietal cortices (Kirkpatrick et al., 2006) or hippocampus (James et al., 2004). Reduced expression of the DISC1 binding partners in the postmortem brain of schizophrenia might suggest a role in the neurodevelopmental pathology of the illness (Lipska et al., 2006). Cannon (2005) hypothesized from

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