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J-ADNIの先行研究としてのJ-COSMIC，SEAD-Japan

J-COSMIC and SEAD-Japan as the precedent studies of J-ADNI

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Summary

アルツハイマー病(AD)の診断における脳血流SPECTとFDG-PETの有用性についてはすでに多くの報告があり，科学的エビデンスが確立されている。また，ADの早期診断についても，脳血流SPECTとFDG-PETは軽度認知障害(MCI)の段階で将来のADへの進展を予測できると期待されているが，エビデンスが不十分とされている。このような状況の中，日本では世界に先駆けてADの早期診断における脳血流SPECTとFDG-PETの有用性に関する科学的エビデンスの確立を目指して2つの前向きコホート研究(J-COSMICとSEAD-Japan)が多施設共同研究として開始されており，その成果が期待されている。

Key words

●軽度認知障害(MCI)
●アルツハイマー病(AD)
●早期診断
●SPECT
●FDG-PET
●コホート研究

1 はじめに

アルツハイマー病(Alzheimer's disease；AD)は物忘れなど記憶障害に関連する自覚症状あるいは周囲からの指摘があって医療機関を訪れ，診断されるのが一般的である。AD診断の基本はNINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association)，DSM-Ⅳ (Diagnostic and Statistical Manual of Mental Disorders，4th edition)などの臨床診断基準に基づく診断であるが，病初期においては臨床診断基準を満たさない場合もある。特に物忘れのみを主訴とする軽度認知障害(mild cognitive impairment；MCI)の段階では数年でADへ進展する症例とMCIで安定している症例を鑑別することは困難である。画像診断，髄液中のτ(タウ)など生物学的マーカー，神経心理検査などによる早期診断が検討されているが，臨床的に確立されているわけではない。根本治療薬の開発とともに早期診断の必要性がますます高まっており，これらの検査法の前向き臨床試験による検証が喫緊の課題である。

ADの診断における脳血流SPECT(single photon emission computed tomography)とFDG-PET(fluorodeoxyglucose-positron emission tomography)の有用性についてはすでに多くの報告があり，科学的エビデンスが確立されている[1]。また，ADの早期診断についても

脳血流SPECTとFDG-PETはMCIの段階で将来のADへの進展を予測できると期待されているが[2)3)]，エビデンスが不十分とされている。

日本では世界に先駆けてADの早期診断における脳血流SPECTとFDG-PETそれぞれの前向きコホート研究J-COSMIC(Japan Cooperative SPECT Study on Assessment of Mild Impairment of Cognitive Function)とSEAD-Japan(Study on Diagnosis of Early Alzheimer's Disease-Japan)が多施設共同研究として開始され，継続中である。本稿ではこれら2つの臨床試験について概要を紹介し，J-ADNI(Japanese Alzheimer's Disease Neuroimaging Initiative)の先行研究としての意義を考察する。

II アルツハイマー病の早期診断に関する前向きコホート研究

J-COSMICとSEAD-Japanは図1に示すような前向きコホート研究である。研究開始から一定期間を症例登録期間とし，MCIの中でも物忘れを主訴とするamnestic MCIの患者を登録し，登録時に脳血流SPECTもしくはFDG-PET，神経心理検査などベースラインのデータを取得する。このうち脳血流SPECTとFDG-PETについてはADを示唆する画像所見の有無について臨床所見を伏せた状態で判定し，記録しておく。登録後3年間の臨床経過観察を行ってADへの移行例と非移行例を確定し，その結果と登録時の画像所見を照合することにより，脳血流SPECTもしくはFDG-PETのMCI時点でのAD発症の予測診断能を算出することができる。本来ならば診断の根拠として病理診断を用いるべきであるが，MCIの場合にゴールドスタンダードとしての病理診断を得ることは疾患の経過から考えても現実的には困難である。このため，便宜的にclinical dementia rating(CDR)で示される認知障害の進行と臨床診断基準(NINCDS-ADRDA)による'probable AD'をエンドポイントとしている。

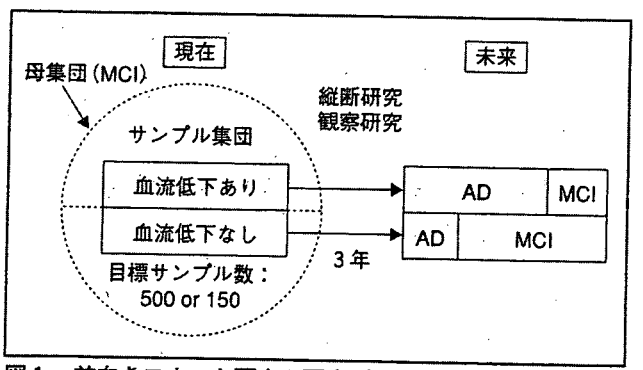

図1 前向きコホート研究の研究デザイン
多施設共同の前向きコホート研究(prospective cohort study)

III J-COSMICについて

わが国では脳血流SPECTの臨床利用が盛んなので，SPECTに関する大規模な臨床試験を実施しやすい環境にある。このため，2003年度から長寿科学振興財団の指定研究として「MCIを対象としたアルツハイマー型認知症の早期診断に関する研究(J-COSMIC)」(研究代表者：現放射線医学総合研究所理事長 米倉義晴)が開始された(表1)。この研究は，MCIを対象としてADの早期診断における脳血流SPECTの役割を明らかにすることを主目的としており，全国41施設が参加している多施設共同の前向き研究(目標症例数500例)である。被験者の選択基準としてはPetersenの定義によるamnestic MCIを基本としている(表2)。MCIからADへの進展を確認するために初回評価後3年間の追跡調査を行い，SPECTの診断能を算出する。同時に神経心理検査の有用性についても検討する。

この研究ではSPECTの解析に共通データベースを利用した画像統計解析(three-dimensional stereotactic surface projection；3D-SSP)が使用される。画像の統計解析を行うには対照データとして正常データベースが必要となるが，これまでは各施設がそれぞれ正常例を集めてデータベースを構築する必要があった。しかし，臨床現場で数を揃えた正常データベースを構築するのは必ずしも容易ではない。したがって共通データベースを用いた診断が可能になれば，3D-SSPの汎用性が高くなり，臨床現場でのADの診断精度の向上に大きく寄与できる。

最終的に319例の登録があり，2007年4月18日現在2

表1　J-COSMICの研究組織

	委員名	役　職	氏　名	施設名
1	研究代表者	研究代表者	米倉義晴	放射線医学総合研究所
2	登録・臨床診断委員会	委員長	福山秀直	京都大学
3		副委員長	鷲見幸彦	国立長寿医療センター
4		委員	朝田　隆	筑波大学
5		委員	森　　敏	松下記念病院
6		委員	荒井啓行	東北大学
7	臨床診断解析委員会	委員長	森　悦朗	東北大学
8		委員	目黒謙一	東北大学
9		委員	北村　伸	日本医科大学武蔵小杉病院
10		委員	羽生春夫	東京医科大学
11	SPECT画像診断委員会	委員長	伊藤健吾	国立長寿医療センター
12		副委員長	松田博史	埼玉医科大学
13		委員	石井一成	兵庫県立姫路循環器病センター
14		委員	桑原康雄	九州大学
15		委員	橋川一雄	大阪南医療センター
16		委員	百瀬敏光	東京大学
17		委員	内田佳孝	千葉大学
18	SPECT画像診断解析委員会	委員長	畑澤　順	大阪大学
19		副委員長	蓑島　聡	ワシントン大学
20	患者保護委員会	委員長	小阪憲司	横浜市立大学

表2　Amnestic MCIの定義

1．記憶障害の自覚，または情報提供者の証言がある
2．記憶障害が年齢に比し客観的に示される
3．全般的な認知機能は正常(MMSE 24以上)
4．日常生活活動は正常
5．認知症ではない(CDR=0.5)

Amnestic MCIは毎年12%がADに移行するが，認知機能低下が緩徐な群，安定な群も含まれる。
(AAN Quality Standards Subcommittee 2001より改変)

年目の追跡調査がほぼ終了して大部分が3年目の追跡調査に入ったところである。すでに60例がエンドポイント(AD以外の認知症を2例含む)に達する一方で，47例が追跡不能となり脱落している。研究グループとしてはこれまでにSPECT画像について読影委員による中央読影，神経心理検査を含む臨床データの解析を行い，登録群の特徴を明らかにしている。縦断的研究であるため，最終結果が出るには時間がかかるが，ADの早期診断における脳血流SPECTの有用性に関するエビデンスの確立が期待される。

Ⅳ SEAD-Japanについて

PETでは用いられる放射性同位元素(陽電子放出核種)は半減期が非常に短く，2分からせいぜい110分であるため，病院内に陽電子放出核種で標識された薬剤をつくるための設備(小型サイクロトロンと自動合成装置)と人員が必要であった。しかし，半減期の比較的長い(110分)^{18}Fで標識された^{18}F-FDGについては放射性医薬品の工場から近隣の病院(自動車で2時間程度の輸送距離まで)へ配送するシステムが整備され，2005年9月からは厚生労働省の認可も受けて，サイクロトロンなど高額の初期投資をしなくてもPETカメラのみの設置で検査が行える状況になった。2007年1月現在で，PETあるいはPET-CTが全国で約330台，サイクロトロンの台数も120台を超えている状況であり，日本国内においても，

PETが臨床的に利用しやすい状態になっている。ただし，日本では，FDG-PETによるADの診断についてまだ健康保険の適用が認められていない。

こうした状況を踏まえ，FDG-PETによるADの早期診断について科学的エビデンスを確立するため，厚生労働科学研究費補助金の長寿科学総合研究事業の一環として「MCIを対象とするアルツハイマー病の早期診断に関する多施設共同研究(SEAD-Japan)」が2005年度から開始された(表3)[6]。

研究の目的は前述のとおりであるが，FDG-PETに加えて，MRI，神経心理検査も総合的に評価する内容でプロトコールが構成されている。研究の概要を図2に示す。目標症例数は統計学的な有意差などを考慮して，150例と設定した。

被験者の選択基準はSPECTの先行研究(J-COSMIC)に準じている(表4)。除外基準ではJ-COSMICと違い，PET検査1ヵ月前に塩酸ドネペジルの投与を受けている患者は除外することになっている(表5)。

表3　SEAD-Japan参加施設

参加施設	代表者氏名	代表者所属部署
国立長寿医療センター	鷲見幸彦	外来診療部
京都大学	福山秀直	高次脳機能総合研究センター
先端医療センター(神戸大学)	千田道雄	分子イメージング研究グループ
県西部浜松医療センター	尾内康臣	先端医療技術センター
東京都老人総合研究所	石井賢二	附属診療所
兵庫県立姫路循環器病センター	石井一成	放射線科
木沢記念病院中部療護センター	奥村　歩	脳神経外科
大悟病院・藤元早鈴病院	三山吉夫	精神科
東北大学	目黒謙一	高齢者高次脳医学

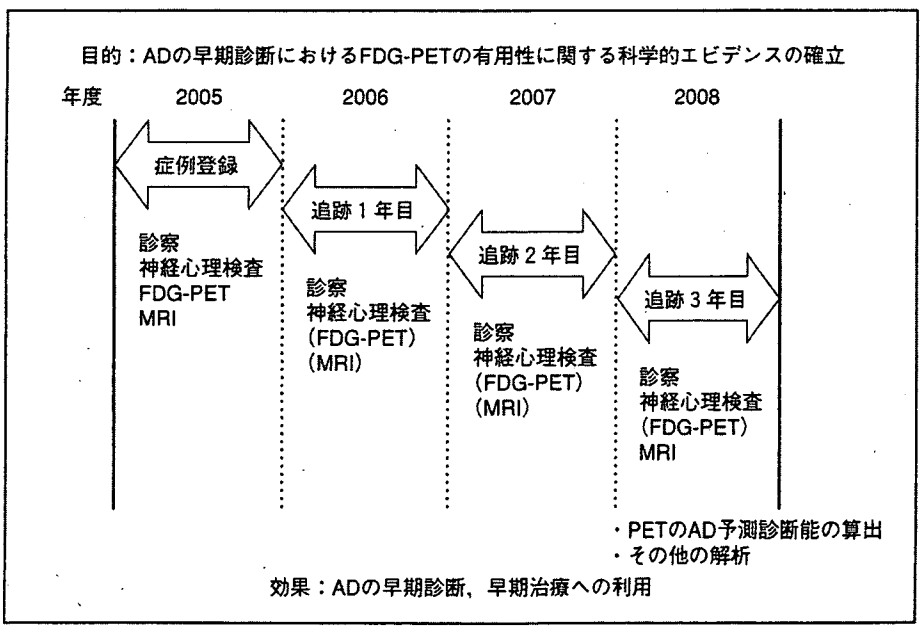

図2　SEAD-Japanの研究概要

表4　SEAD-Japanの症例選択基準

選択基準
軽度認知障害(amnestic MCI)患者でFDG-PET，MRI，神経心理検査を実施可能な患者。性別は問わないが，上限は79歳までとする。

軽度認知障害患者の選択規準
1．Amnestic MCI
2．明らかな神経疾患，精神疾患を認めない
3．神経学的症候(片麻痺，錐体外路徴候，球麻痺，運動失調，眼球運動障害，失語，失行，失認，半側空間無視，痙攣発作など)を認めない
4．精神医学的徴候(うつ，幻覚，妄想など)を認めない(GDS 10点以下)

GDS：geriatric depression scale

表5　SEAD-Japanの症例除外基準

除外基準
1．アルコール中毒の既往または治療中の患者
2．てんかんの既往または治療中の患者
3．教育歴が6年以下
4．症状を評価しうる情報提供者が存在しない
5．インスリン治療中の糖尿病患者
6．抗うつ薬，向精神薬，長期にわたる催眠鎮静薬(抗不安薬を含む)の投与を受けている患者
7．PET検査前1ヵ月以内に塩酸ドネペジルの投与を受けている患者
8．重篤な合併症(悪性腫瘍，心不全，肝障害，腎障害，内分泌疾患など)

PET検査については，J-COSMICと同様に3D-SSPによる統計画像の読影を行う。

SEAD-JapanではMRIも並行して評価する。MRIに関しては3DのT$_1$強調画像，T$_2$強調画像，FLAIR画像の撮像を行い，初回登録時と3年間の経過終了時のMRI検査を必須にしている。MRIの読影については，視覚的な評価に加えて，画像統計解析を行う。症例ごとにvoxel-based morphometryによる脳萎縮の定量評価を行うとともに，3年間の経過観察後，AD進展群と非進展群の間で脳萎縮の群間比較なども行う。

研究実施体制その他について紹介する。臨床試験に関するデータの収集，管理などは研究者が行わず，第三者機関で行うことが研究の客観性その他を担保するうえで望ましいとされている。この研究では大学病院医療情報ネットワーク研究センター(UMINセンター)にデータサーバを置いて，データの収集，蓄積，管理などを行うシステムを構築している。症例登録は，これまでのようにファックスその他の媒体を使った登録ではなく，インターネット経由で登録するシステムを採用している。各施設では，インターネット経由で登録フォームを開いて順番に入力することにより，登録の可否が自動的に判定される。そしていったん登録すれば取り消しはできない。

また，臨床試験登録をUMINセンターで行っているので，SEAD-Japanに関する内容を日本語と英語で参照することができる。

最後に研究進捗状況であるが，2007年3月末までで115例が登録された。2007年6月30日現在，約3分の1の症例が1年目の追跡調査の期限を迎えている。

V　J-ADNIの先行研究としてのJ-COSMIC，SEAD-Japanの意義

米国では現在，より大規模な前向き臨床試験が進行中であり，2005年から北米50施設が参加して；ADNI(Alzheimer's Disease Neuroimaging Initiative)が始まっている[5]。この試験は，MCI 400例，AD 200例，正常200例という大規模な症例集積を行って，ADの早期診断のみならず，進行評価におけるMRI，PET，生物学的マーカーの有用性を確立することを目的としている。今後のAD治療薬の臨床治験の精度向上，効率化のために総合的な評価システムの確立を最終目標としている。ADNIではADを評価する代替指標(サロゲートマーカー)としての画像，生物学的マーカーの標準化を世界的規模で行うことを目指しており，そのためわが国でもJ-ADNIとして今年から研究が開始されることは別稿のとおりである。

では，すでに実施中のJ-COSMIC，SEAD-JapanはJ-ADNIの先行研究としてどのような意義があるのか。

J-COSMICについてはPETに比してより汎用性の高い脳血流SPECTの研究であることから，研究成果をより広い範囲で活用することが可能である。また，画像を中心として多数例のMCIを対象とした前向きコホート研究を実施するうえでのノウハウは，その後の研究を実施するうえで貴重な財産となっている。J-COSMICとSEAD-Japanはほぼ同一の患者選択基準を使用しているので，AD発症の予測診断能についてFDG-PETの結果と比較することで脳血流SPECTの有用性と限界が明らかになる。

SEAD-JapanとJ-ADNIは重点の置き方に差異があるものの，共通してFDG-PETとMRIを評価の対象としている。SEAD-Japanでは参加施設が認知症のPETについて経験の豊富な9施設であり，画像検査としての品質管理が容易である。そのような施設からMCIのみを対象に症例を集め，主にAD発症の予測診断に目標を絞って主にFDG-PETの有用性を検討する研究であり，ADの早期診断に向けてのエビデンスの確立はSEAD-Japanで達成可能である。

一方，J-ADNIでは正常例，MCI，ADを網羅して多数例を集めるとともにAD発症の予測診断だけでなく，進行評価も対象にする。また，PET以上にMRIに重点が置かれるとともに，遺伝子検索を含む生物学的マーカーの確立も大きな柱であり，より網羅的な大規模研究である。PETについてはFDG-PETに加えてアミロイドイメージングも行うのでFDGとは性質の異なる画像を検討することになる。さらにJ-ADNIでは研究成果をより広く普及させるために画像検査の標準化，品質管理を大きな課題としている。

Ⅵ まとめ

J-COSMIC，SEAD-JapanはJ-ADNIの先行研究としてそれぞれ独自の意義を有しており，その成果が期待されるとともにJ-ADNIの実施につながる多くのノウハウを提供すると考えられる。

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Social cognition and frontal lobe pathology in schizophrenia: A voxel-based morphometric study

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Impaired social cognition in schizophrenia is considered as the core contributor in the poor psychosocial functioning of schizophrenic patients. In this study, in order to better understand the neurobiological processes underlying social dysfunction in schizophrenia, we investigated regional structural brain abnormalities and emotion-attribution abilities in these patients. Twenty schizophrenic patients and 20 group-matched healthy comparison participants underwent magnetic resonance imaging (MRI) and were examined for emotion-attribution abilities by using the Perception of Affect Task (PAT). Voxel-based morphometry (VBM) was applied to investigate regional brain structural alterations. Relative to the healthy participants, the schizophrenic patients exhibited reduced gray matter concentrations in the left superior temporal gyrus, the medial prefrontal cortex (MPFC), right anterior cingulate gyrus, bilateral ventrolateral prefrontal cortex, and right insula. The schizophrenic patients performed poorly on emotion-attribution tasks. Importantly, poor performance on emotion attribution to protagonists in social situations was found to be associated with reductions in gray matter in the MPFC of the patient group. This preliminary result suggests that in schizophrenia, difficulties in understanding the emotional experiences of others are possible manifestations of structural abnormalities in the MPFC. This study provides the neurobiological correlates of social dysfunction in schizophrenia and links structural abnormalities with impaired social cognitive abilities.

Keywords: Schizophrenia; Social cognition; Emotion attribution; VBM; Frontal lobe

Introduction

Schizophrenia is a psychiatric disorder associated with poor social functioning. The highlights of its core symptomatology include diminished social or emotional reciprocity and failure to construct appropriate relationships. Recent studies have focused on facial emotion processing abilities in schizophrenia because of the importance of faces as a medium of social communication among humans (Darwin, 1872). These studies demonstrate that schizophrenic patients show impaired recognition of negative facial expressions (Mandal et al., 1998). In addition to the critical role of emotion processing, mentalizing abilities, often referred to as the theory of mind (ToM; Premack and Woodruff, 1978), are equal constituents of the important aspects of human social interactions. ToM abilities have been widely investigated in individuals with schizophrenia. These studies indicate that such individuals are not adept at understanding the beliefs or intentions of other individuals (Brune, 2005).

Numerous neuroimaging and neuropsychological studies have found evidence that the amygdala and the orbitofrontal cortex make important contributions to facial expression processing (Adolphs et al., 1994; Hornak et al., 1996) and the medial and orbital frontal cortex, to ToM-related tasks (Baron-Cohen et al., 1994; Fletcher et al., 1995; Gallagher et al., 2000; Vogeley et al., 2001). These brain regions and the bank of the superior temporal sulcus constitute the "social brain" proposed by Brothers (1990), and both intact facial emotion processing and good mentalizing abilities are required for successful social interaction. Therefore, the point at which neuroimaging and neuropsychological studies converge with the recent findings of schizophrenia studies is the possible functional or structural disruption of the neural mechanisms underlying the social cognitive abilities in schizophrenia.

Meanwhile, brain volume studies have begun to show regional volume alterations in individuals with schizophrenia. Disproportionate reduction in the gray matter in the frontal and temporal lobes is the main consensus obtained from these studies (Shenton et al., 2001). These regional volume alterations have been found to be related to psychopathology such as positive and negative symptoms (Gur et al., 2000; Sanfilipo et al., 2000) and also to various cognitive deficits such as executive function, attention, and memory (Antonova et al., 2004). Although several other structures, such as corpus callosum, cerebellum, or thalamus, have also been reported to be altered in schizophrenia (Shenton et al., 2001), the

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frontal and temporal lobes are key regions involved in social cognition and could also contribute to some of social deficits observed in schizophrenia.

To date, social cognitive abilities and structural brain alterations in individuals with schizophrenia have not been directly compared, although researchers have begun to realize the importance of understanding the neural basis of social cognitive deficits in delineating social impairments in schizophrenia (Pinkham et al., 2003). In this study, we employed voxel-based morphometry (VBM; Ashburner and Friston, 2000) to investigate regional gray matter abnormality and examined its relationship with emotion-attribution abilities in schizophrenic patients. We applied the tasks that require attributing emotions to facial expressions (i.e., emotion expression recognition), which have been often used in schizophrenia research (e.g., Edwards et al., 2002). Further, we applied tasks that require attributing emotions to protagonists in social situations. The latter task examines the ability to recognize the emotional experiences of others within a social context, which would recruit a broader range of social cognitive factors, including perspective taking or empathy. Thus, investigating emotion recognition with a test battery, involving various types of social components, should help in improving our understanding of social cognitive deficits in individuals with schizophrenia.

It was predicted that: 1) brain abnormalities in schizophrenia detected by VBM would be the areas underpinning social behavior, as well as the regions reported by previous anatomical studies; 2) patients with schizophrenia would present specific social cognitive deficits in the emotion attribution tasks; 3) in the event that the two abovementioned hypotheses are true, we should observe the specific association between abnormalities of social brain structures and social cognitive deficits in schizophrenia.

Method

Participants

The schizophrenia group comprised 20 patients (10 men and 10 women), referred to the Department of Psychiatry, Kyoto University Hospital. Based on the Structural Clinical Interview for DSM-IV (SCID), each patient fulfilled the DSM-IV criteria for schizophrenia [paranoid ($n=11$), disorganized ($n=5$), catatonic ($n=2$), schizophreniform ($n=2$)]. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). All patients were receiving antipsychotic medication [typical ($n=3$), atypical ($n=16$), typical and atypical ($n=1$)] and were physically healthy at the time of scanning and psychological tests. None had a history of head trauma, neurological illness, serious medical or surgical illness, substance abuse, or any first relatives who had had psychotic episodes.

The comparison group comprised 20 healthy individuals (10 men and 10 women) who were matched with the schizophrenia group with regard to age and education level. These subjects were also evaluated on the basis of SCID. None had a history of neurological or psychiatric illness, or any first relatives who had had psychotic episodes.

Table 1 presents demographic information. The estimated verbal and performance IQ were obtained from vocabulary and block design subtasks, respectively, in the Wechsler Adult Intelligence Scale-Revised (WAIS-R) by transforming the scores corrected for age into *T* scores.

After a complete description of the study to the participants, written informed consent was obtained from them. This study design was approved by the Committee on Medical Ethics of Kyoto University.

Tasks

The participants' basic visuoperceptual ability for facial stimuli was examined using a short version of the Benton Facial Recognition Test (BFRT; Benton et al., 1983). The participants matched the faces of identical individuals from six choices, which were shown in varying views and light conditions.

To examine the participants' ability to attribute emotions to facial expressions and to protagonists in complex social situations, we administered the Perception of Affect Task (PAT; Rau, 1993), comprising four subtasks designed to separately assess verbal,

Table 1
Demographic, clinical, and neuropsychological characteristics of the participants

	Schizophrenia ($n=20$)		Healthy ($n=20$)		Statistics	
	Mean	S.D.	Mean	S.D.	t ($df=38$)	P
Age (years)	38.8	7.2	39.1	7.1	0.13	NS
Sex (male/female)	10/10		10/10		–	–
Handedness (right/left)	19/1		19/1		–	–
Education years	13.5	2.0	14.4	1.9	0.15	NS
Age at onset (years)	27.4	6.4	–	–	–	–
Duration of illness (years)	11.6	8.7	–	–	–	–
Drug (mg/day, haloperidol equivalent)[a]	10.9	8.7	–	–	–	–
PANSS Total	64.5	19.8	–	–	–	–
PANSS Positive	16.4	6.7	–	–	–	–
PANSS Negative	15.7	6.5	–	–	–	–
PANSS General	32.4	10.1	–	–	–	–
VIQ	97.8	16.0	107.5	14.8	1.998	NS
PIQ	97.8	14.9	107.0	12.7	2.11	$P=0.04$
BFRT	45.5	6.03	47.2	4	1.02	NS

Abbreviations: PANSS = Positive and Negative Syndrome Scale, VIQ = the estimated verbal IQ obtained from the subtask of vocabulary in the Wechsler Adult Intelligence Scale-Revised (WAIS-R) by transforming scores corrected for age into *T* scores, PIQ = the estimated performance IQ obtained from the subtask of block design in the WAIS-R by transforming scores corrected for age into *T* scores, BFRT = Benton Facial Recognition Test.

[a] Haloperidol equivalents were calculated according to Inagaki (2004).

visual, and verbal–visual processing abilities. The following are their details.

Subtask 1

The participants were presented with short stories describing emotional situations. From a list of seven emotion labels (happiness, sadness, fear, anger, disgust, surprise, and neutral), they were asked to choose the one that best described the feeling of the main protagonist in each situation. A total of 35 stories were designed such that each of these emotions could be elicited from five stories.

Subtask 2

The participants were provided with a list of seven emotion labels (happiness, sadness, fear, anger, disgust, surprise, and neutral) and were requested to choose the label that best described the emotional facial stimuli presented. Five faces for each of these emotions were selected from the Picture of Facial Affect series (Ekman and Friesen, 1976); thus, there were 35 face stimuli in total.

Subtask 3

The participants were again presented with the same 35 short stories as in subtask 1. This time, they were provided with a list of seven facial expressions (happiness, sadness, fear, anger, disgust, surprise, and neutral) of one individual from the Picture of Facial Affect series and were asked to choose the facial expression that best described the feeling of the main protagonist in each situation.

Subtask 4

The participants were provided with seven photographs of social situations. The human figures representing one of seven emotions (happiness, sadness, fear, anger, disgust, surprise, and neutral) were indicated by an arrow in each social situation. The faces of these figures were erased or were not observable. For each of the same 35 facial stimuli used in subtask 2, the participants were requested to choose the human figure that best described the emotional facial stimuli presented.

These subtasks were performed in this fixed order for all the participants.

MRI acquisition and pre-processing

All the participants received MRI scans from a 3-T whole-body scanner equipped with an 8-channel phased array coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 4.38 ms; TR = 2000 ms; TI = 990 ms; FOV = 256; slice plane = axial; slice thickness = 1 mm; resolution = 0.94 × 0.94 × 1.0; and slice number = 208. To increase the signal/noise ratio, we scanned all the participants three times and obtained average images from the three images by using statistical parametric mapping 2 (SPM2) software (The Wellcome Department of Imaging Neuroscience, London, U.K.) running in Matlab 6.5 (The MathWorks, Natick, MA, U.S.A.).

The images were analyzed using the optimized VBM methods described in detail by Ashburner and Friston (2000) and Good et al. (2001). We used an extension of SPM, the VBM tools written by Christian Gaser (http://dbm.neuro.uni-jena.de/vbm). Briefly, a study-specific whole brain template and gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) prior images were created from all the participants. Using these customized template and priors, each participant's original image was then spatially normalized and segmented into GM, WM, and CSF, according to the optimized protocol. The images were resliced with $1 \times 1 \times 1$ mm^3 voxels. The procedure yielded two types of GM images-modulated and unmodulated. The former were used for the group comparison of voxel-wise GM volume (GMV) differences, whereas the latter, for GM concentration (GMC). In this study, we analyzed both modulated and unmodulated data. The resultant GM images were smoothed with a Gaussian kernel of 12 mm full width at half maximum, on which all the analyses were performed.

Data analyses

Social cognitive task performance

Data were analyzed using repeated measures analyses of variance (ANOVA) with repeated-measures factors SUBTASK (4 levels) and EMOTION (7 levels) and the between-subjects factor GROUP (2 levels). In addition, planned contrasts univariately assessed for each subtask whether there was a significant difference between the two groups. For analyses assessing repeated measures effects, violations of the sphericity assumption were considered by correcting degrees of freedom according to Huynh-Feldt (Vasey and Thayer, 1987). Finally, in order to test a priori hypotheses about group differences for negative emotions in the facial expression recognition, which were reported by several schizophrenic studies (Mandal et al., 1998; Edwards et al., 2002), linear contrasts were computed with specific error variances in subtask 2 (Boik, 1981). Analyses were computed using SPSS v.12.0 and Statistica (Stat Soft, Inc, 1998). Statistical significance was defined as $P \leq 0.05$.

Regional gray matter reductions in patients relative to controls

To identify the brain regions wherein the schizophrenic patients showed reductions in GMV or GMC relative to the healthy participants, an analysis of covariance (ANCOVA) was undertaken in SPM2. Global gray matter volume was included as a nuisance covariate in the analysis. Output was in the form of the statistical parametric maps (SPMs), based on a voxel-level height threshold of $P < 0.05$ (corrected for multiple comparisons using the false discovery rate [FDR; Genovese et al., 2002]) and an extent threshold of 600 contiguous voxels.

Correlation analyses

Using the "VOI (Volume Of Interest)" function (spm_regions.m) in SPM2, each patient's GMCs or GMVs were extracted for each cluster of concentration or volume reduction produced by above-mentioned procedures.

The correlation analyses in SPSS v.12.0 were used to investigate the structure–symptom relationship between the patients' GMC/GMV in regions of reduction and their PANSS scores (Positive, Negative, and General scores) and the structure–social cognition relationship between the GMC/GMV and PAT scores (subtasks 1, 2, 3, and 4). Parametric statistics were used if an initial exploration of the data set suggested normal distribution; nonparametric statistics were applied otherwise.

Results

Demographic and basic neuropsychological data

There were no significant differences in age, education, and the estimated VIQ between the schizophrenic patients and the healthy

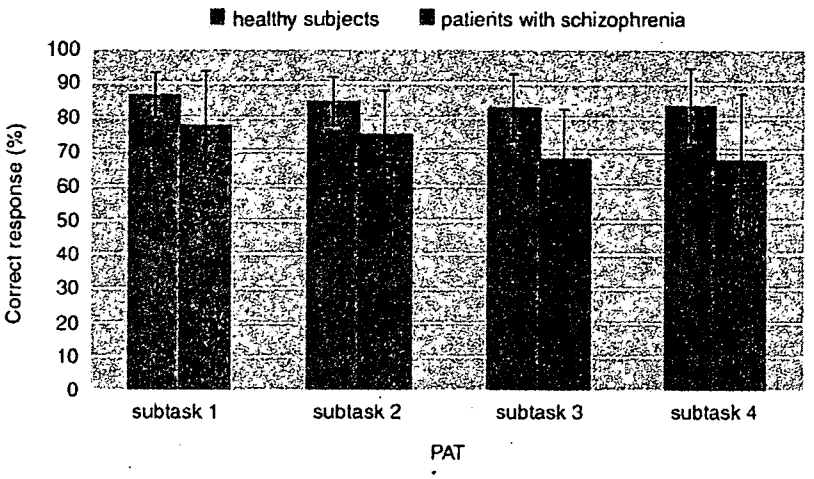

Fig. 1. Mean (±standard deviation) of the proportion of correct response on each subtask of PAT in patients with schizophrenia and healthy participants.

participants (Table 1). The estimated PIQ was worse in the schizophrenic patients than in the healthy participants.

Behavioral measures

Benton Facial Recognition Test

There was no significant difference between the schizophrenic patients and the healthy participants in the BFRT (Table 1).

Perception of Affect Task

The ANOVA revealed significant main effects: GROUP ($F(1, 38)=14.88$, $P<0.001$), SUBTASK ($F(3, 114)=5.38$, $\varepsilon_{HF}=1$, $P<0.02$), and EMOTION ($F(6, 228)=32.77$, $\varepsilon_{HF}=0.95$, $P<0.001$), a significant interaction between SUBTASK and EMOTION ($F(18, 684)=16.22$, $\varepsilon_{HF}=0.875$, $P<0.001$). No significant interaction was found between GROUP and SUBTASK ($P=0.184$), between GROUP and EMOTION ($P=0.482$), or a three-way interaction ($P=0.424$). Planned contrasts revealed significantly lower scores in the patients group for all of the four subtasks: subtask 1 ($F(1,38)=5.138$, $P<0.05$), subtask 2 ($F(1,38)=8.908$, $P<0.01$), subtask 3 ($F(1,38)=15.23$, $P<0.001$), and subtask 4 ($F(1,38)=10.05$, $P<0.01$) (Fig. 1).

Linear contrast testing a priori hypotheses that the schizophrenic patients would show specific deficits in recognizing negative facial expressions (fear, anger, disgust, and sadness) as compared to non-negative emotional expressions was not significant ($P=0.126$). Another linear contrasts assessing whether patients showed specific deficits in recognizing certain facial expressions revealed that the schizophrenic patients were significantly less accurate than the healthy participants in recognizing surprised ($F(1,38)=5.63$, $P=0.023$) and angry facial expressions ($F(1,38)=5.033$, $P=0.031$). No significant differences were found for the other emotional expressions.

Regional gray matter reductions in patients relative to controls

The schizophrenic patients showed reduced GMC relative to the healthy controls (Table 2, Fig. 2a) in left superior and middle temporal gyri, the medial prefrontal cortex (MPFC), right anterior cingulate gyrus, bilateral inferior frontal gyri, and right insula.

There were no regions wherein the patients exhibited reduced GMV relative to the controls. Therefore, the correlation analyses mentioned below were performed using the patients' regional GMC data.

Correlation analyses

Structure–symptom relationship

The Kolmogorov–Smirnov tests showed normal distribution of structural data (right anterior cingulate gyrus $P>0.05$, all other areas $P>0.2$), and that of symptom data (negative scores $P>0.05$, all other scores $P>0.2$). No significant statistical correlation was found, but there was a trend between the MPFC and negative symptoms (Pearson's $r=-0.403$, $P=0.078$).

Structure–social cognition relationship

The Kolmogorov–Smirnov tests showed normal distribution of subtasks 1 ($P>0.2$), subtask 2 ($P>0.1$), and subtask 3 ($P>0.2$), but not that of subtask 4 ($P=0.006$). A significant positive correlation was found between the MPFC and subtask 4 (Spearman's $r=0.464$, $P<0.05$) (Figs. 2b,c), indicating that with a greater MPFC concentration reduction, the accuracy with which subtask 4 was performed was less. Since the patients group was inferior in the estimated PIQ, the abovementioned correlation could be simply

Table 2
The regions of gray matter concentration reduction in patients with schizophrenia relative to healthy participants

Anatomical region	Brodmann's Area	Cluster centers[a]			Cluster size
		x	y	z	
Left superior and middle temporal gyri	BA21/22	−57	−17	−8	1424
Medial frontal gyrus	BA10	5	56	−3	3353
Right anterior cingulate gyrus	BA25	2	7	−6	1460
Right inferior frontal gyrus	BA47	36	24	−10	2176
Left inferior frontal gyrus	BA11/47	−39	48	−15	658
Right insula	BA13	34	−25	15	1477

[a] Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

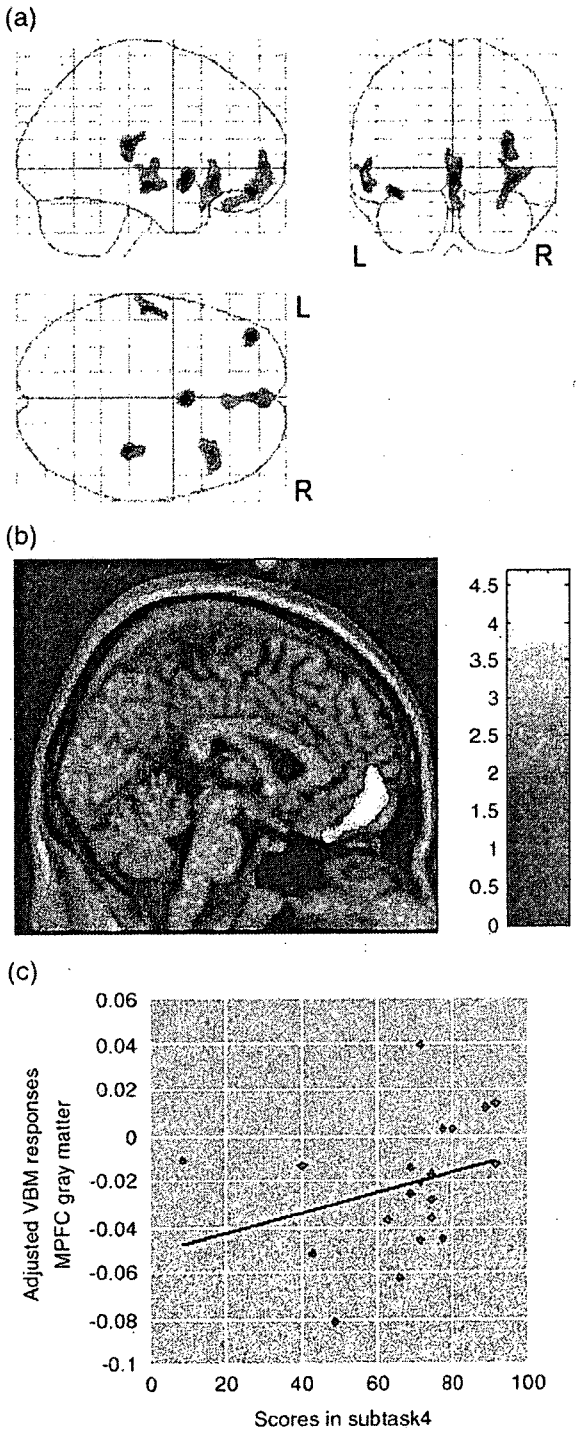

Fig. 2. (a) Gray matter concentration reductions in patients with schizophrenia were displayed on a glass brain. (b) Reduced concentration in the medial prefrontal cortex of patients with schizophrenia. (c) Adjusted concentration in the MPFC plotted against the scores in subtask 4 in patients with schizophrenia.

abscriable to the variation of the PIQ. However, such a possibility was eliminated because no significant correlation was found between the estimated PIQ scores and subtask 4 scores in the patients group (Spearman's $r=0.377$, $P>0.1$). No other relationship was observed between regional GMCs and PAT scores (all comparisons: $P>0.1$).

Discussion

This study mainly aimed to explore the relationship between regional gray matter abnormality and social cognition in individuals with schizophrenia. The results yielded three main findings.

First, the behavioral task revealed that the ability to attribute emotions to facial expressions and to the story protagonists is significantly compromised in schizophrenic patients. Impaired emotion recognition observed in subtask 2 is compatible with previous reports (Mandal et al., 1998). In contrast to several other studies (Johnston et al., 2001), intact processing of facial configurations in BFRT in our patients suggested that deficits in facial expression processing in schizophrenic patients are specific to the emotional component. Furthermore, it is possible that this is specific for certain negative emotions, with the greatest difficulty in recognizing fear, and to some extent, anger or sadness (Mandal et al., 1998; Edwards et al., 2002). Our results indicated that schizophrenic patients were less accurate than healthy participants in recognizing surprised and angry expressions. There was no significant difference between groups on fear identification, although fearful expressions were poorly recognized by schizophrenic patients, which might reflect the difficulty with which fearful expressions are recognized (Ekman and Friesen, 1976).

In subtasks 1, 3, and 4, the participants were presented with verbal or nonverbal scenarios depicting various social situations and were asked to identify the emotion of the main protagonists. The schizophrenic patients were markedly affected in these tasks; this is similar to the observations of previous studies in which various ToM-related tasks were repeatedly applied and defective ToM performances by schizophrenic patients were demonstrated (Brune, 2005). However, in contrast to the ToM tasks in the previous studies, which mainly examined cognitive mental attribution, i.e., intentions or beliefs, our tasks focused more on the emotional component of mental attribution, in other words, empathetic ToM. Indeed, some researchers have begun investigating the possible fractionation of functional requirements of cognitive ToM and empathetic ToM (Hynes et al., 2006; Vollm et al., 2006). However, these two aspects (i.e., ToM and empathy) do not have to be mutually distinctive but can also share some subcomponents. Notably, it was postulated that, a decoupling computational mechanism between self and other plays a critical role in both ToM and empathic understanding (Decety and Jackson, 2004; 2006). This would be further advanced by future studies. Based on the results of the present study, it appears likely that schizophrenic patients have more general deficits in representing the emotional states of others rather than a simple perceptual deficit in decoding emotional signals displayed by others.

The second finding of this study is the concentration reductions in the multiple frontal and temporal lobe structures, i.e., the MPFC, bilateral inferior frontal gyri, right anterior cingulate gyrus, left superior and middle temporal gyri, and right insula, in schizophrenic patients. In a recent meta-analysis of VBM studies conducted by Honea et al. (2005), reductions in the left superior and middle temporal gyri were most robustly observed in schizophrenic patients, followed by reductions in frontal lobes and insula, with which the present findings are consistent.

The third main finding of the present study is that among these abovementioned regions, we observed a specific association only between the MPFC abnormality and emotion-attribution deficit in schizophrenic patients. A number of neuroimaging and neuropsychological studies have indicated that the representation of mental states of others incorporates the MPFC (Brunet et al., 2000; Fletcher et al., 1995; Gallagher et al., 2000; Stone et al., 1998; Stuss et al., 2001; Vogeley et al., 2001). The relationship between the MPFC and emotion attribution in the present study would be in agreement with these earlier findings: the more pronounced the structural abnormalities of the MPFC, the greater is the impairment of the mentalizing ability. This view is also in line with the PET activation study that demonstrated abnormal activation within the MPFC during a ToM task in schizophrenic patients (Brunet et al., 2003).

However, as mentioned above, there appear to be functional and anatomical fractions in the ToM-related processes: cognitive ToM-attribution of cognitive states- and empathetic ToM-attribution of emotional states. These possible fractionations were directly investigated only very recently. Wider areas of activation in the MPFC in cognitive and empathetic ToMs have been demonstrated, using verbal (Hynes et al., 2006) or nonverbal scenarios (Vollm et al., 2006). Although some regions were activated in both the cognitive and the empathetic ToM, the ventral segments of the MPFC were activated strongly in the empathetic ToM. This region roughly corresponded to the abnormal concentration observed in the present study. Therefore, in contrast to the general mental attribution that is processed in the dorsal MPFC, the ventral sector could be associated with emotional components embedded in social interaction that would be particularly relevant to the empathetic aspects. Thus, based on the present findings, it may be speculated that the structural abnormalities of the ventral MPFC–the possible key structure for the empathetic ToM–underlie impaired emotional processes in real-life social interactive situations observed in schizophrenia.

The reason why only subtask 4 showed an association with the MPFC concentration clearly necessitates further investigation; nevertheless, one interpretation may be feasible. Although there appears to be general consensus that the MPFC plays a major role in social cognition, some authors assert that the role of the MPFC becomes particularly critical when the stimulus contains an explicit social context that can be directly identified (Vollm et al., 2006; Walter et al., 2004). Given that the same applies to the current findings, the photographs of actual social scenes used in subtask 4, which surpass subtasks 1 and 3 in explicitness or directness, may explain the selective association between this task and the MPFC abnormality.

The present study suggested only a weak association between clinical symptoms and the structural abnormalities. Further studies may discover a structure–symptom relationship by categorizing the clinical symptoms in a more scrutinized manner such as in Liddle's tripartite model of schizophrenic symptomatology (Liddle, 1987). Another limitation of the present study is that we obtained a significant group difference in the analysis of GMC but not in that of GMV. These two analyses are considered to detect the different aspects of GM abnormalities (Good et al., 2001); thus, the reason why one analysis yielded a significant difference whereas the other did not need further investigation. Moreover, even though we found the interesting association between the MPFC and a social cognitive task, we did not correct it for multiple comparisons. Thus, we should take this conclusion as a preliminary one, though it would be expected for future studies by focusing on specific brain regions under specific hypothesis to verify the finding observed here. Finally, our tasks used static pictures as stimuli, but real-life social interactions are usually held in a dynamic way. Further experiments would be warranted to confirm the observed effect by using dynamic stimuli such as video-clips (Gross and Levenson, 1995) or moving faces (Yoshikawa and Sato, 2006).

In conclusion, the present study has exhibited a clear evidence of impaired social cognition in schizophrenia. Schizophrenic patients were impaired in attributing emotions not only to facial expressions but also to the story protagonists, which suggested general deficits in interpreting the emotional states of other people. Most importantly, it was demonstrated that the deficit in emotion attribution involving a social situation was correlated with concentration reductions in the MPFC of these patients. In this study, the possible link between social cognitive deficit and regional brain abnormality has been elucidated for the first time. This finding will help us to better characterize the nature of social dysfunctioning in schizophrenia and will further validate the neural basis of social cognition.

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ORIGINAL PAPER

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Insular volume reduction in schizophrenia

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Abstract Structural and functional abnormalities of the insular cortex have been reported in patients with schizophrenia. Most studies have shown that the insular volumes in schizophrenia patients are smaller than those of healthy people. As the insular cortex is functio-anatomically divided into anterior and posterior subdivisons, recent research is focused on uncovering a specific subdivisional abnormality of the insula in patients with schizophrenia. A recent ROI-based volumetric MRI study demonstrated specific left anterior insular volume reduction in chronic schizophrenia patients (Makris N, Goldstein J, Kennedy D, Hodge S, Caviness V, Faraone S, Tsuang M, Seidman L (2006) Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res 83:155–171). On the other hand, our VBM-based volumetric study revealed a reduction in right posterior insular volume (Yamada M, Hirao K, Namiki C, Hanakawa T, Fukuyama H, Hayashi T, Murai T (2007) Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. NeuroImage 35:292–298). In order to address these controversial results, ROI-based subdivisional volumetry was performed using the MRI images from the same population we analyzed in our previous VBM-study. The sample group comprised 20 schizophrenia patients and 20 matched healthy controls. Patients with schizophrenia showed a global reduction in insular gray matter volumes relative to healthy comparison subjects. In a simple comparison of the volumes of each subdivision between the groups, a statistically significant volume reduction in patients with schizophrenia was demonstrated only in the right posterior insula. This study suggests that insular abnormalities in schizophrenia would include anterior as well as posterior parts. Each subdivisional abnormality may impact on different aspects of the pathophysiology and psychopathology of schizophrenia; these relationships should be the focus of future research.

Key words schizophrenia · insular · volumetry · self-awareness

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Introduction

It has been postulated that dysfunction of the limbic system would be linked to difficulties in distinguishing between internal and external perceptions and regulating behaviors, ultimately allowing the emergence of the psychotic symptoms of schizophrenia; however, the underlying pathology remains to be elucidated [2, 9, 27]. The insular cortex is part of the limbic region, playing a key role in integrating perceptual experiences and affects to produce balanced behavior [1, 16].

There is converging evidence of a functio-anatomical abnormality of the insula in patients with schizophrenia. Functional neuroimaging studies suggest that insular hypometabolism [6] or decreased cerebral blood flow [4] might be involved in the pathophysiology of schizophrenia. Volumetric magnetic resonance imaging (MRI) studies of the insular cortex have almost unanimously indicated that there are morphological abnormalities of the insular gray matter in patients with schizophrenia [7, 10, 14, 18–21, 24, 25, 27].

However, what remains unsolved is whether the insular abnormality in schizophrenia is specific to a certain subdivision (or lateralized), or if it is bilateral and global. Regarding the laterality issue, the literature is inconsistent: some studies report bilateral insular volume reductions [10, 14, 20, 25], whereas others report left-sided volume reductions [19, 21, 24]. Right-sided insular volume reduction has also been reported in female subjects [7].

In addition to the laterality issue, what is important is the intrahemispheric functio-anatomical subdivision of the insular cortex. The insular cortex is anatomically divided into two major subdivisions (anterior and posterior lobules) by the central sulcus of the insula [22, 23]. Morphological separation between these two parts reflects, to some extent, the characteristics of the cytoarchitectonic composition and their different neural connections. The anterior insula represents the agranular and adjacent dysgranular insula, and is connected to the piriform, orbitofrontal, temporopolar and parahippocampal regions. Together with the above-mentioned areas, the anterior insula plays a role in the control of emotions and autonomic regulation. By contrast, the posterior insular lobule consists of the granular and adjacent regions, and is more closely connected to the somatosensory, auditory, and motor areas [17]. The posterior insula mainly connects with the primary and secondary somatosensory cortices (SI, SII), the superior and inferior parietal lobules, the orbitofrontal, prefrontal and premotor cortices, the auditory cortex (AI, AII), the superior and inferior temporal cortices, the basal ganglia and the thalamus [1, 17].

Makris et al. [15] recently measured the volumes of the insular subregions (left/right × anterior/posterior) using the central sulcus of the insula as a landmark for subdivisions, and investigated the volumetric alteration of the insula in patients with schizophrenia based on a volumetric MRI study. The authors reported that there was a significant reduction in insular cortical volume throughout the anterior insular lobules, and particularly in the left anterior lobule, in chronic schizophrenia patients compared with normal controls.

However, there are technical problems in previous volumetric MRI studies. Since the insula is a relatively small structure, it is difficult to clearly delineate it in images of low spatial resolution, especially when subdivisional volumetry is intended. Most studies have utilized lower magnetic field MR images (from 1.0 to 1.5 T) and obtained slices thicker than 1 mm (~1.5–3 mm). Such low quality protocols might lead to insufficient measurement of insular volumes.

Previously, our voxel-based morphometry (VBM) study revealed that there is a volume reduction in the right posterior insular lobules of patients with schizophrenia [26], in contrast to the results of Makris et al. [15]. Thus, to address these controversial results, a region-of-interest (ROI)-based subdivisional volumetry study was performed using the MRI images from the same population we analyzed in our previous VBM-study [26]. The analyzed structural MRI images were obtained using a 3.0 T MRI scanner with slices of an acceptable thickness (1 mm) to investigate changes in the volumes of the subdivisions of the insular cortex.

Methods

Participants

The participants are identical to those of our previous study [26]. The schizophrenia group comprised 20 patients (10 men and 10 women), referred to the Department of Psychiatry, Kyoto University Hospital. Exclusion criteria included a history of seizure disorder, head trauma resulting in a loss of consciousness, neurological illness or substance abuse. Based on the Structural Clinical Interview for DSM-IV (SCID), all patients met DSM-IV criteria for schizophrenia and clinical symptoms were rated according to the Positive and Negative Syndrome Scale (PANSS; [13]). All patients were being treated with antipsychotic medications and were physically healthy at the time of scanning. Haloperidol equivalents, which were calculated according to Inagaki et al. [11], were administered at 11.9 ± 8.9 mg/day. Among the 20 patients, 18 were being treated with atypical antipsychotic medications (12 with 6.63 ± 3.45 mg/day of risperidone, 5 with 10.00 ± 6.12 mg/day of olanzapine, 3 with 391.7 ± 278.8 mg/day of quetiapine, and 2 with 18.00 ± 6.00 mg/day of perospirone): 11 were being treated with a single atypical antipsychotic medication, three were being treated with multiple atypical antipsychotics, and four were being treated with atypical antipsychotics in combination with typical (haloperidol or chlorpromazine) antipsychotics. Two patients were being treated with multiple typical antipsychotics. Some patients (n = 8) were also receiving adjunctive anticholinergic treatment. The comparison group comprised 20 healthy individuals (10 men and 10 women) who were matched with the schizophrenia group with regard to age and education level. These subjects were also evaluated on the basis of SCID. They had no current or past history of psychiatric or neurologic diseases. In addition, they had no first degree relatives who had current or past psychotic episodes.

Table 1 indicates the demographic characteristics of the two groups. The estimated verbal and performance IQs were obtained from vocabulary and block design subtasks, respectively, using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) by transforming the scores corrected for age into T scores.

After a complete description of the study to the participants, they gave written informed consent to a protocol approved by the Committee on Medical Ethics of Kyoto University.

MRI acquisition and pre-processing

MR images were obtained at Kyoto University Hospital on a 3-T whole-body scanner equipped with an 8-channel phased array coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 4.38 ms; TR = 2000 ms; TI = 990 ms; FOV = 240; slice plane = axial; slice thickness = 1 mm; resolution = 0.94 × 0.94 × 1.0; and slice number = 208. In order to increase the signal/noise ratio, we scanned all participants three times and obtained average images from the three scans using statistical parametric mapping 2 (SPM2) software (The Wellcome Department of Imaging Neuroscience, London, U.K.) running in Matlab 6.5 (The Math Works, Natic, MA, U.S.).

Table 1 Demographic, clinical, and neuropsychological characteristics of the subjects

	Schizophrenia ($n = 20$)		Healthy ($n = 20$)		Statistics	
	Mean	S.D.	Mean	S.D.	t (df = 38)	p
Age (years)	38.8	7.2	39.1	7.1	0.13	$p > 0.05$
Sex (male/female)	10/10		10/10		–	–
Handedness (right/left)	19/1		19/1		–	–
Education years	13.5	2.0	14.4	1.9	0.15	$p > 0.05$
Age at onset (years)	27.4	6.4	–	–	–	–
Duration of illness (years)	11.6	8.7	–	–	–	–
Drug (mg/day, haloperidol equivalent)	11.9	8.9	–	–	–	–
PANSS Total	64.5	19.8	–	–	–	–
PANSS Positive	16.4	6.7	–	–	–	–
PANSS Negative	15.7	6.5	–	–	–	–
PANSS General	32.4	10.1	–	–	–	–
VIQ	97.8	16.0	107.5	14.8	2.00	$p > 0.05$
PIQ	97.8	14.9	107.0	12.7	2.11	$p = 0.04$

ROI definition

The boundaries of the insular cortex were manually determined using MRIcro (Chris Rorden, University of Nottingham, Great Britain) on consecutive coronal slices. The most rostral coronal plane 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, following the procedure of Crespo-Facorro et al. [3]. In addition, following the procedure applied by Makris et al. [15], the central sulcus of the insula was considered as the landmark dividing the insular cortex into anterior and posterior parts; thus, this sulcus constitutes the inferior border of the anterior insular lobule and the superior border of the posterior insular lobule (Fig. 1). The volume of each lobule was calculated by multiplying the number of voxels assigned to that structure by the single-voxel volume $0.94 \times 0.94 \times 1.0$ mm^3. All measurements were carried out by the first author (TS) who was blind to subjects' identity, demographic data, diagnosis, and psychopathology.

To determine the reliability of the insular measurements, 10 subjects were randomly selected. Segmentation and parcellation was independently carried out by the first author and another researcher who was experienced at volumetric analysis. Both raters were blinded to participant details, including the study group and

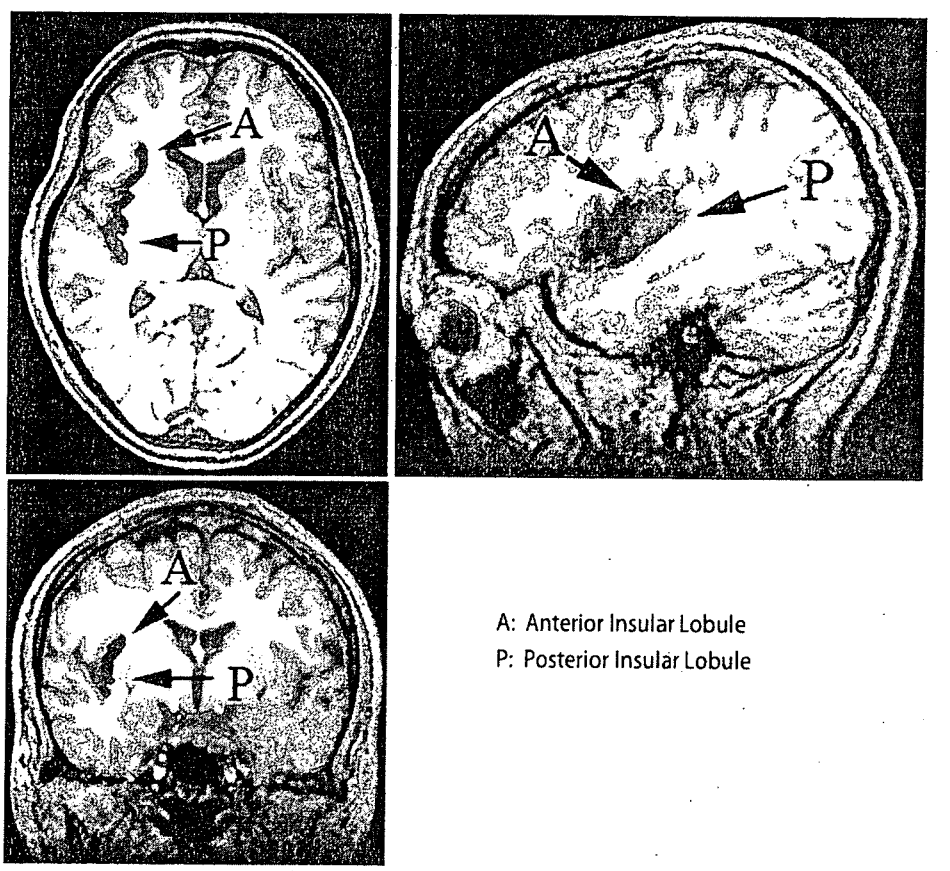

Figure 1 The anterior and posterior insular lobules

the results of neuropsychological tests, during the measurement. For the insula subregion, intrarater reliability ranged from 0.96 to 0.97; interrater reliability ranged from 0.90 to 0.92 using Cronbach's alpha coefficient.

Intracranial volume (ICV) measurement

Estimates of the global gray and white matter volumes and cerebrospinal fluid (CSF) volume were obtained after the automatic brain segmentation procedure had been carried out by SPM2 in our previous study [26]. Total ICV was the sum of the volumes of gray and white matters and CSF.

Statistical analysis

In group comparisons of the insular subdivisional gray matter volumes, the relative volume ([absolute ROI volume/ICV] × 100) was analyzed by repeated measures analysis of variance (ANOVA) with group (schizophrenia, control) as a between-subject factor, and hemisphere (left, right) and subregion (anterior, posterior) as within-subject variables. As mentioned in the introduction, each insular subdivision differs in its anatomical features, connectivity and functional roles. Thus, we were also interested in determining if the volumes of each insular subdivision differ significantly between the groups, especially for those of the left anterior and right posterior subdivisions, the volumes of which have been reported to be reduced in schizophrenia patients [15, 26]. Hence, separate group comparisons for each of the four subregional volumes were performed without correction for multiple comparisons of the four subregions.

Finally, in order to investigate the relationship between the gray matter volumes of the patients' insular subregions and their PANSS scores, parametric statistics were used if an initial exploration of the data set indicated a normal distribution; otherwise nonparametric statistics were applied.

For all of the resulting statistics, the significance threshold was set at $p < 0.05$. All of the above statistical analyses were performed using SPSS v.12.0.

Results

Demographic and clinical characteristics of patients and controls

Demographic and clinical data are summarized in Table 1. Two-tailed t-tests were applied to compare the differences in demographic and clinical variables between groups. The groups did not differ significantly in age, sex, handedness, education or estimated VIQ. The estimated PIQs of the schizophrenia subjects were significantly worse than those of healthy controls [controls = 107.0 (12.7); patients = 97.8 (14.9); $t = 2.11$; df = 38; $p = 0.04$].

Volume change

The ANOVA revealed a significant main effect of group (F = 4.280, df = 38, $p = 0.045$), subregion (F = 677.4, df = 38, $p < 0.001$) and a hemisphere-by-subregion interaction (F = 8.825, df = 38, $p = 0.005$), but no significant main effect of hemisphere (F = 0.019, df = 38, $p = 0.890$) and no significant group-by-hemisphere (F = 0.086, df = 38, $p = 0.771$), group-by-subregion (F = 0.041, df = 38, $p = 0.840$), or group-by-hemisphere-by-subregion (F = 1.027, df = 38, $p = 0.317$) interactions. This result suggests that patients with schizophrenia have a global (that is, non-specific to subregion or hemisphere) reduction in the volume of insular gray matter relative to healthy subjects. When subregional relative volumes were compared between groups separately, a significant difference was demonstrated only in the right posterior lobule (F = 4.960, df = 38, $p = 0.032$), but not in the other three subregions (Table 2 and Fig. 2).

Table 2 Insular volumes in subjects with schizophrenia and healthy controls

	Schizophrenia ($n = 20$)		Healthy ($n = 20$)		Statistics	
	Mean	S.D.	Mean	S.D.	t (df = 38)	p
Intracranial volume (ml)	1564.1	212.8	1617.3	172.3	0.87	0.39
Insular cortex volume						
Right anterior						
Absolute (ml)	3.5	0.59	3.5	0.35		
Relative (%)	0.23	0.029	0.22	0.027	−1.00	0.33
Right posterior						
Absolute (ml)	1.9	0.40	1.8	0.30		
Relative (%)	0.13	0.021	0.11	0.015	−2.20	0.032
Left anterior						
Absolute (ml)	3.7	0.59	3.6	0.47		
Relative (%)	0.24	0.029	0.22	0.026	−1.50	0.13
Left posterior						
Absolute (ml)	1.8	0.33	1.7	0.19		
Relative (%)	0.11	0.017	0.11	0.015	−1.20	0.24

Correlations between volumes and clinical measures

Age, age when first medicated, duration of medication treatment, or current dose of antipsychotic medication, were not correlated with any of the investigated relative volumes. No significant correlation was demonstrated between any of the investigated relative volumes and any of the three PANSS subscores (positive, negative and general scores).

Discussion

Three main findings emerge from this study: (1) schizophrenia patients show a global reduction in insular volumes; (2) among insular subregions, the right posterior insula was the only subregion in which patients showed a significant volume reduction; (3) in the patient group, none of the subregional insular volumes were associated with psychopathological measures.

Insular volume reduction in schizophrenia

Although, most previous studies have shown volume reduction in the insular gray matter in patients with schizophrenia, little is known regarding the subdivi-

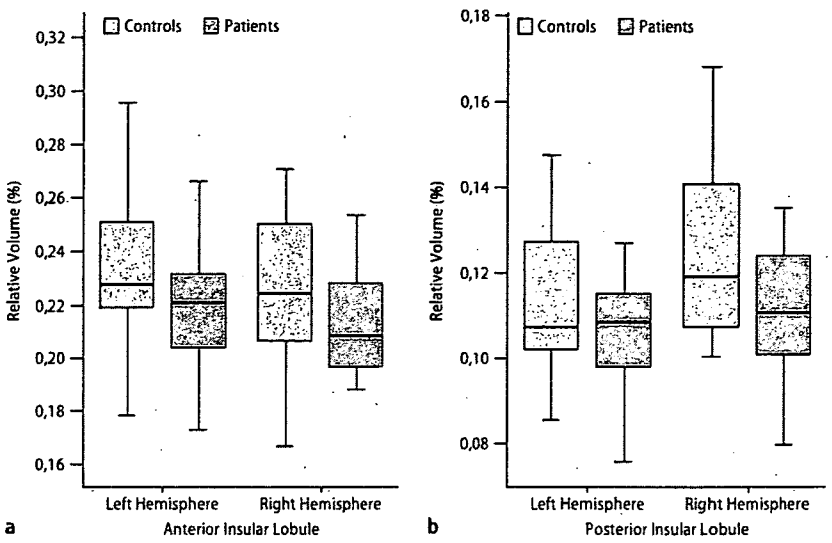

Figure 2 Box-plots of the relative volumes (%) of the insular lobules in the anterior (a) and posterior (b) zones of patients with chronic schizophrenia (n = 20) and healthy control subjects (n = 20). Means are indicated by horizontal lines. Each box encompasses 50% of the distribution of volumes

sional specificity of this volume reduction, as summarized in the Introduction. Our results, using high spatial resolution images, suggest that the insular abnormality is not subregion specific, but global, affecting the structure bilaterally as well as in both anterior and posterior subregions. Thus, the inconsistencies of the previous literature might be due to differences in patient characteristics as well as substantial measurement error variations associated with lower resolution images.

Specifically, in contrast to the recent study by Makris et al. [15], which is, other than our studies, the only study to investigate the insular subregional volumes in schizophrenia by dividing the insula into anterior and posterior sections, we did not demonstrate a specific volume reduction in the left anterior insula. This discordance might originate from differences in the characteristics of the patients investigated; for example, the illness durations in the patients in Makris' study (22.5 ± 10.9 years) were twice as long as those in ours (11.6 ± 8.7 years). However, the difference in methodological protocols would also be important. We traced an average of 50 coronal slices per subject when measuring the insular cortex; among these, 30 covered the posterior insular cortex. We believe that this method, using 1 mm-thick slices, can provide a more exact measure of the subregional volumes than that of Makris et al. [15], using 3 mm-thick coronal slices.

Although we did not demonstrate a statistically significant group difference in left anterior insular volumes, our assertion is not that the left anterior insula is not involved in the pathophysiology of schizophrenia, but that the left anterior insula is not specifically involved. Anterior and posterior subdivisions of the insula are involved in different neural circuitries, and bear a differential impact on our cognition and behavior. We suspect that the functions of both subdivisions would be compromised in schizophrenia. Pathology of the anterior insula, together with other limbic and paralimbic structures, mainly affects emotional processes modulating our behaviors. Pathology of the posterior subdivision would have a different impact.

Regarding the effect of medication on regional volumes, we found no significant correlation between antipsychotic doses and subdivisional insular volumes. Dazzan et al. [5] reported that typical but not atypical antipsychotics are likely to induce regional cortical volume reductions, including a volume reduction in the insula, among first episode schizophrenia patients. The lack of an association of medication with insular volumes in our current study might be due to the fact that most of the patients were being treated with atypical antipsychotics.

The volume change in the right posterior lobule

The main result of our analysis should be interpreted as a global reduction in the volume of the insula. However, in a separate group comparison for each subdivision, the only subregion in which a significant difference in volumes was found was the right posterior insula, although this difference was marginal without correction for multiple comparisons. Comparing the methodological advantages and disadvantages of VBM and manual ROI analysis, Kubicki et al. [14] recommended the initial use of VBM in an exploratory manner and subsequent confirmatory analyses by application of manual ROI tracing. Such an approach has been demonstrated to be successful in our analysis regarding the insular cortical volumes of schizophrenia: an initial whole-brain VBM analysis revealed a reduced volume region in the right posterior part of the insula [26], and this preliminary result was further confirmed by the present analysis using manual ROI tracing.

Although not fully elucidated, recent neuroimaging studies provide a clue to the possible functional sig-

nificance of this particular subregion of the human insula. Based on a lesion study analyzing an unselected sample of stroke patients with right brain damage, Karnath et al. [12] reported that right posterior insula lesions are specifically associated with "anosognosia" for hemiplegia/hemiparesis. On the other hand, in an activation study by Farrer et al. [8] using positron emission tomography (PET), healthy subjects were requested to indicate whether movements they saw on a computer screen corresponded to their executed movements, or were controlled by another person. The experiment showed decreased activity in the right posterior insula with a decreasing feeling of controlling the movement; that is, when subjects experienced a mismatch between what they did and what they saw. By contrast, this activity was increased when the afferent input matched their own actions. A possible interpretation of these findings is that the right posterior insula plays an important role in integrating signals related to self-awareness and establishing a boundary between self and others.

Although speculative, considering the functional significance of this region, some of the core characteristics of the psychopathology of schizophrenia could be explained by a dysfunctional right posterior insula: lack of insight could be explained straightforwardly as compromised self-awareness, while multimodal hallucinations could also be interpreted as a consequence of misintegration of sensory inputs into self-awareness.

Unfortunately, we did not find any correlation between psychopathological measures and the volume of any of the insular subregions, including the right posterior insula. The small sample size or non-uniformity of the subjects investigated (including both first episode subjects and more chronic subjects) might have affected our results of non-association between psychopathology and insular volumes. However, previous studies are also controversial regarding the association of psychopathology and insular volume reduction. If the above-mentioned role of the right posterior insula and its possible impact on psychopathology are true, such a putative association could be demonstrated using specifically-designed cognitive tasks or psychopathological measures to capture aspects of self-awareness in schizophrenia; this is the goal of our future studies.

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