とは考えにくいが，偽証罪があることを念頭に置いた方がよい．

II．責任能力

犯罪をおかした精神障害者について刑罰を特別に軽くする慣行は洋の東西を問わず古来から存在した．フランスでは1810年刑法のデマンス(démence)の規定，イギリスでは1843年のマクノートン準則，ドイツでは1871年刑法の「自由な意思決定の欠如」が近代の責任能力規定の基礎をなす．責任とは違法な行為について行為者を道義的に非難しうることで，「責任なければ刑罰なし」という責任主義は近代刑法の基本原則とされる．

日本の刑法第39条は「心神喪失者の行為は，罰しない．心神耗弱者の行為は，その刑を減軽する．」と定めている．責任無能力者を指す法律上の文言が「心神喪失者」，限定責任能力者が「心神耗弱者」である．明治時代に法律が整備される過程で，民法の禁治産，準禁治産での心神喪失，心神耗弱の語が刑法にも取り入れられた．民法でいう心神喪失は精神障害により自己の利害得失に関する判断能力を欠くことであり，是非善悪を弁識する能力である刑法上の心神喪失とは異なる．大審院判決（1931年）は心神喪失を「精神の障礙に因り事物の理非善悪を弁識する能力なく又は此の弁識に従て行動する能力なき状態」，心神耗弱をこれらの能力の「著しく減退せる状態」と定義した．

このように責任能力は〈精神障害〉〈是非の弁識能力〉〈行動の制御能力〉から構成され，精神障害の有無や性質は“生物学的要素”，弁識と制御の能力の程度は“心理学的要素”と呼ばれる(誤解されやすい用語であるが慣用されている)．ドイツや日本ではこれら2つの要素を総合して判断する“混合法”が採用されている．

心神喪失と心神耗弱は法律概念であり，最高裁判所の判決もこれについての判断は裁判所に委ねられると明言している．そうすると鑑定人の任務は法的判断のための医学的資料を提供するにとどまることになる．しかし責任能力に関して踏み込んだ意見が鑑定人に求められるのが実情である．筆者は便宜上，「鑑定人の立場での参考意見」と断った上で責任能力についても鑑定書に記載することにしている．

III．医療観察法

正式名称は「心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律」である．措置入院では触法精神障害者への対応が不十分であることなどを理由に2005年7月から施行されている．重大な他害行為（殺人，放火，強盗，強姦，強制わいせつ，傷害）を行い，心神喪失または心神耗弱を理由に不起訴処分か裁判で無罪または刑の減軽（刑期のあるものを除く）を受けた者について検察官は地方裁判所へ申立てを行う（傷害以外については未遂も含む）．

裁判所は2ヶ月を超えない鑑定入院を行う（1ヶ月以内の延長可能）．鑑定医は鑑定結果に本法による医療の必要性に関する意見を付す．厚生労働科学研究班の『鑑定ガイドライン』によれば，医療観察法鑑定は，①対象者が精神障害者であるか否か，②医療観察法の医療必要性，を明らかにする．医療必要性は疾病性，治療反応性，社会復帰要因のいずれもが一定水準を上回ることで認定されるとしている．

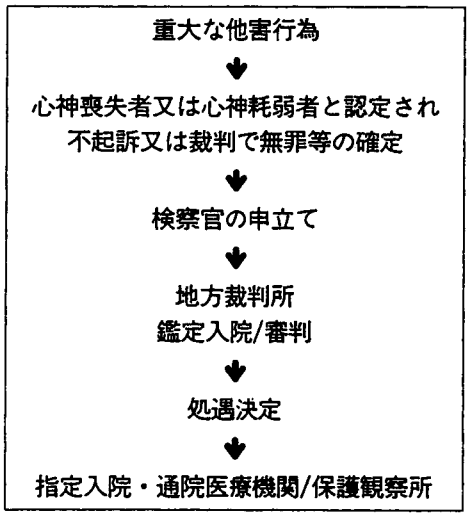

図1　医療観察法の概要

表2 成年後見制度の概要

類型	対象者	援助者	診断
後見	精神上の障害により事理を弁識する能力を欠く常況にある者	成年後見人	鑑定
保佐	上記の能力が著しく不十分な者	保佐人	鑑定
補助	上記の能力が不十分で後見または保佐の要件に当たらない者	補助人	診断書*
任意後見	判断能力低下に備えて予め契約	任意後見人	診断書*

* 必要に応じて鑑定

審判は裁判官，精神保健審判員各1名の合議で，必要に応じ精神保健参与員の意見を聴く．鑑定結果に基づいて処遇の要否と内容を決定する．すなわち，①対象行為を行った際の精神障害を改善し，これに伴って同様の行為を行うことなく，社会に復帰することを促進するため，入院をさせてこの法律による医療を受けさせる必要があると認める場合：医療のため入院させる決定．②この法律による医療を受けさせる必要が認められるが①に当たらない場合：入院によらない医療を受けさせる決定．③上記のいずれにも当たらない場合：この法律による医療を行わない決定．④申立てが不適法と認める場合：申立ての却下．

医療は指定入院医療機関及び指定通院医療機関で行う．入院によらない場合，対象者は精神保健観察に付され，保護観察所の社会復帰調整官が必要な指導などを講ずる．退院または入院継続は医療機関の管理者が保護観察所長の意見を付して，処遇の終了と再入院は保護観察所の長が医療機関の管理者と協議の上，裁判所に申立て，裁判所が決定を行う．

医療観察法の制定に伴って設けられた医師の資格，役職は精神保健判定医と精神保健審判員である．厚生労働大臣は政令によって精神保健審判員の職務を行うのに必要な学識経験を有する医師（精神保健判定医）の名簿を最高裁判所に送付する．地方裁判所はこの名簿に記載された者のうち毎年あらかじめ選任した者の中から処遇事件ごとに精神保健審判員を任命する．審判員の主な任務は裁判官とともに合議体を開き，評議で意見を述べることであり，精神医学の専門家として裁判官と対等の立場で決定に与る重要な役割を負う．

Ⅳ．成年後見制度

民法では「心神喪失の常況にある者」について家庭裁判所が禁治産を宣告することができ，禁治産者は後見に付して，禁治産者の行為は取り消すことをできると規定した．また「心神耗弱者及び浪費者」については準禁治産者として保佐人を付することをできるとした．社会の高齢化に押されて禁治産宣告が急増した結果，画一性，取り消さない限り禁治産者であり続けること，本人に告知されないこと，戸籍への記載，親族間の紛争の道具として濫用されやすいことなど，種々の弊害が認識されるようになった．

このような背景のもとで2000年4月から面目を一新した成年後見制度が施行されている．法改正はノーマライゼーションの理念に沿い，自己決定の尊重と残存能力の活用や柔軟かつ弾力的な利用しやすさを目指した．表2に示すように，旧制度での禁治産，準禁治産の2本立てから，後見，保佐，補助の3類型（法定後見）に加えて任意後見が設けられ，選択肢が増えている．対象者の能力障害の程度に応じて，自己決定の範囲と援助者に委ねられる権限（同意権，取消権，代理権など）の範囲がきめ細かく定められている．

申立ては本人，配偶者，4親等内の親族等であり，家裁調査官による調査を経て，後見と保佐では原則として鑑定が，補助と任意後見では診断書が必要である．家裁での審判を経て告知され，開

始される．鑑定書と診断書の作成のために最高裁判所事務総局から「手引」が発行されている．成年後見の対象者の多数を高齢者が占めるが，知的障害及び統合失調症その他の精神障害で判断能力の不十分な成年者ももちろん対象となる．

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腕試し問題

問1．精神衛生法(1950年)と精神保健福祉法(1995年)の「法律の目的」の主な相違点は何か．

問2．次の事例で，主治医が入院を勧めたところ，患者がA，Bの2通りの反応をしたと想定する．それぞれについて選択肢の中から適当なものを選び，その理由を説明せよ．

33歳の主婦．妄想型統合失調症．2度の入院歴があり，現在まで同じ医師が主治医を務めている．6か月前に寛解状態で退院した．2か月前から服薬が不規則となり，興奮や自傷はないが，不眠がちで，話しかけても上の空となった．病状の悪化を心配した夫に付き添われて来院した．診察には応じるが，表情が硬く，緊張がうかがわれる．質問にはおおむね答えるが，時に幻聴に注意を奪われ，小声の独語を発する．夫は入院を希望している．

【A】主治医が「しばらく入院して治療しましょう」と告げたところ，患者はうなづいて承諾の意思表示をした．理由を問うと，「自分は病気ではないけれど，入院しなさいという(幻覚の)声が聞こえるから」と答えた．入院の目的を説明したが，態度は変わらなかった．

①任意入院とする．　②医療保護入院とする．

【B】主治医が「しばらく入院して治療しましょう」と告げたところ，患者は首を横に振って拒否の意思表示をした．理由を問うと，「先生が言われることはわかりますが，育児から手が離せませんから」と，生活上の理由をあげた．さらに説得したが，態度は変わらなかった．

①入院は行わない．　②医療保護入院とする．

問3．日本の刑法は精神障害者の責任能力をどのように規定しているか．

問4．刑事事件の被疑者・被告人について行われる精神鑑定の種類と手続を説明せよ．

問5．医療観察法において検察官が地方裁判所への申立てを行わなければならない場合の要件は何か．

問6．医療観察法は申し立てられた対象者について裁判所は医師に鑑定を命じ，鑑定医は「この法律による入院による医療の必要性に関する意見」を鑑定結果に付さなければならないと定めている．次の事例ではどのような意見が考えられるか．

26歳の男性．会社員の家庭で養育され，内気な性格で非行はなかった．中学の終わり頃から腋臭を気にした．高校を卒業し，親元から離れて予備校に通った．浪人中も腋臭が気になった．2年後に大学に入学したが，友人たちが何か隠しているように感じ，通学が苦痛になり，退学した．常に疎外感を抱き，単身で職を転々とした．家族との接触も避けるようになった．対象行為の半年前，「隣人からマインドコントロールされる」という体験があり，隣家の窓に石を投げた．「車を運転していると前方の車がわざと急ブレーキをかける」と感じ，護身用ナイフを持ち歩くようになった．精神科治療歴はない．対象行為は，電車内でいきなり無関係の男性にナイフで切りつけ，全治2週間の傷害を負わせたもの．警察で動機を問われると，「理由は被害者に聞けばわかる」な

どと奇妙な発言に終始した．起訴前鑑定では被害関係妄想，幻聴，被影響体験，性格変化を症状とする妄想型統合失調症と診断され，不起訴処分とされて医療観察法の申立てがなされた．医療観察法鑑定では，陰気，寡黙で，差しさわりのない会話には応じるが，質問が妄想体験や対象行為に触れると急に硬い表情になって黙りこんだ．

問7．成年後見制度にはどのような類型があるか．それぞれどのような対象者に適用されるか．

問8．次はアルツハイマー病の事例である．(1)～(5) に当てはまる言葉は何か．

5年程前から物忘れがひどくなり，勤務先の直属の部下を見ても誰かわからなくなるなど，次第に社会生活を送ることができなくなった．日常生活においても，家族の判別がつかなくなり，その症状は重くなる一方で回復の見込みはなく，2年前から入院している．ある日，本人の弟が突然事故死し，本人が弟の財産を相続することになった．弟には負債しか残されておらず，困った本人の妻が (1) のために，(2) の審判を申し立てた．家庭裁判所の審理を経て，本人について (3) が開始され，夫の財産管理や身上監護をこれまで事実上担ってきた妻が (4) に選任され，妻は (5) の手続をした．(最高裁判所「成年後見関係事件の概況」から改変して引用)

問9．中毒者を診断したときの医師の届出義務は「麻薬及び向精神薬取締法」と「覚せい剤取締法」でどのように規定されているか．

問10．刑法及び精神保健福祉法は守秘義務をどのように定めているか．

【第15回専門医制度委員会企画・腕試し問題解答】

問1：4)	問4：5)	問7：3)	問10：1)，5)
問2：1)，5)	問5：2)，3)	問8：4)，5)	
問3：5)	問6：1)，5)	問9：2)	

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Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis

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Common abnormalities within the schizophrenia spectrum may be essential for the pathogenesis of schizophrenia, but additional pathological changes may be required for the development of full-blown schizophrenia. Clarifying the neurobiological similarities and differences between established schizophrenia and a milder form of schizophrenia spectrum disorder would potentially discriminate the pathophysiological mechanisms underlying the core features of the schizophrenia spectrum from those associated with overt psychosis. High-resolution MRIs were acquired from 25 patients with schizotypal disorder, 53 patients with schizophrenia and 59 healthy volunteers matched for age, gender, handedness and parental education. Volumetric measurements of the medial temporal structures and the prefrontal cortex subcomponents were performed using consecutive 1-mm thick coronal slices. Parcellation of the prefrontal cortex into subcomponents was performed according to the intrinsic anatomical landmarks of the frontal sulci/gyri. Compared with the controls, the bilateral volumes of the amygdala and the hippocampus were reduced comparably in the schizotypal and schizophrenia patients. The parahippocampal gyrus volume did not differ significantly between diagnostic groups. Total prefrontal grey matter volumes were smaller bilaterally in the schizophrenia patients than in the controls and the schizotypal patients, whereas the schizotypal patients had larger prefrontal grey matter than the controls in the right hemisphere. In the schizophrenia patients, grey matter volumes of the bilateral superior frontal gyrus, left middle frontal gyrus, bilateral inferior frontal gyrus and bilateral straight gyrus were smaller than those in the controls. The schizophrenia patients also had reduced grey matter volumes in the right superior frontal gyrus, bilateral middle frontal gyrus and right inferior frontal gyrus relative to the schizotypal patients. Compared with the controls, the schizotypal patients had larger volumes of the bilateral middle frontal gyrus and smaller volumes of the right straight gyrus. There were no significant between-group differences in volumes of the ventral medial prefrontal cortex or the orbitofrontal cortex. These findings suggest that volume reductions in the amygdala and hippocampus are the common morphological substrates for the schizophrenia spectrum, which presumably represent the vulnerability. Additional widespread involvement of the prefrontal cortex in schizophrenia may lead to the loss of inhibitory control in other brain regions and suggests (although it is not specifically be related to) its critical role in the manifestation of overt psychosis.

Keywords: schizotypal disorder; schizophrenia; MRI; medial temporal lobe; prefrontal cortex

Abbreviations: BA = Brodmann area; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10 = International Classification of Diseases, 10th edition; ICV = intracranial volume; MANCOVA = multivariate analysis of covariance; ROI = region of interest; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; VBM = voxel-based morphometry

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Introduction

Pathological deviations genetically and phenomenologically related to schizophrenia are grouped under the schizophrenia spectrum. This concept reflects the assumption that schizophrenia has a multifactorial aetiology in which multiple susceptibility genes interact with environmental insults to yield a range of phenotypes (Siever and Davis, 2004). Common neurobiological abnormalities in the schizophrenia spectrum may be essential for the pathogenesis of schizophrenia. However, some additional pathological changes may also be required for the development of full-blown schizophrenia. Schizotypal (personality) disorder is thought to be a prototypic disorder within the schizophrenia spectrum (Siever *et al.*, 2002). It is genetically related to schizophrenia (Siever *et al.*, 1990; Kendler *et al.*, 1993) and characterized by odd behaviour and attenuated forms of the features seen in schizophrenia without manifestation of overt and sustained psychosis (World Health Organization, 1993; American Psychiatric Association, 1994). Clarifying the neurobiological similarities and differences between established schizophrenia and schizotypal (personality) disorder would potentially discriminate the pathophysiological mechanisms underlying the core features of the schizophrenia spectrum from those associated with overt psychosis. Thus, this strategy may provide a clue to the mechanisms underlying the development of schizophrenic psychosis.

Convergent evidence suggests that the pathological process in schizophrenia predominantly affects the frontotemporolimbic-paralimbic regions (Shenton *et al.*, 2001; Suzuki *et al.*, 2002). The hippocampal formation and the prefrontal cortex are two of the major structures that have received the most attention in the search for the neural substrate of schizophrenia. Slight but significant volume reductions in the hippocampus, amygdala and frontal lobe have been reported in a number of volumetric MRI studies of schizophrenia (see reviews: Lawrie and Abukmeil, 1998; Harrison, 1999; Shenton *et al.*, 2001). Dysfunction of these regions has been implicated in the cardinal characteristics of schizophrenia. Involvement of the hippocampal formation has been suggested to play a role in manifesting psychotic symptoms and verbal memory deficits in schizophrenia patients (Friston *et al.*, 1992; Liddle *et al.*, 1992; Goldberg *et al.*, 1994), while prefrontal abnormalities have been related to negative symptoms and cognitive impairments, such as deficits in working memory, executive and problem solving functions (Goldman-Rakic and Selemon, 1997).

There is increasing evidence of alterations in the brain structures of schizotypal subjects (see reviews: Dickey *et al.*, 2002*a*; Siever and Davis, 2004). Our previous study using voxel-based morphometry (VBM) demonstrated that grey matter reduction in the medial temporal region was common to patients with schizophrenia and schizotypal disorder, but schizophrenia patients showed more widespread involvement of the frontal lobe than schizotypal subjects (Kawasaki *et al.*, 2004). These findings need to be confirmed by detailed volumetric region of interest (ROI) analyses. However, only a single volumetric study, by Dickey and colleagues (Dickey *et al.*, 1999), has examined the medial temporal lobe structures in schizotypal subjects and found no abnormality in the amygdala or hippocampus volume. Previous MRI studies have provided evidence of preserved volume of the brain structures densely interconnected with the prefrontal cortex in schizotypal subjects relative to schizophrenia (Byne *et al.*, 2001; Takahashi *et al.*, 2002*b*, 2004; Suzuki *et al.*, 2004). These findings suggest that the prefrontal cortex may be structurally spared in schizotypal subjects. As to the prefrontal cortex *per se*, however, only preliminary data referring to preserved frontal lobe volume in schizotypal patients have been reported (Siever and Davis, 2004). Siever and Davis (2004) have made an extensive review of neurobiological findings in subjects with schizotypal personality disorder and proposed a model regarding the pathophysiology of the schizophrenia spectrum disorders. Their model also predicted that temporal volume reductions would be common across the schizophrenia spectrum disorders, whereas frontal volumes would be more preserved in schizotypal subjects than in schizophrenia patients. More data on the volume changes of both the medial temporal lobe and the prefrontal cortex in schizotypal subjects are needed for comparison with those in schizophrenia patients. Detailed volumetric analyses of both structures in the same subjects would allow more compelling conclusions to be drawn. In addition, the great multiplicity of structural and functional organization within the prefrontal cortex necessitates examination of the structural alterations in each subcomponent of the prefrontal cortex. This has been conducted in several studies of schizophrenia patients (Wible *et al.*, 1997; Buchanan *et al.*, 1998, 2004; Goldstein *et al.*, 1999; Crespo-Facorro *et al.*, 2000; Convit *et al.*, 2001; Yamasue *et al.*, 2004) but has never been reported for schizotypal subjects.

The present study aimed to elucidate the implications of structural abnormalities of the medial temporal structures and the prefrontal cortex in the manifestation of psychosis in schizophrenia. We employed high-resolution MRI and performed volumetric assessments of the amygdala, hippocampus, parahippocampal gyrus and prefrontal cortex in patients with schizotypal disorder, comparable patients with established schizophrenia and healthy control subjects. The prefrontal cortex was subdivided into subcomponents according to the intrinsic anatomical landmarks. We hypothesized, from our previous VBM findings (Kurachi, 2003*a*, *b*; Kawasaki *et al.*, 2004) and the model by Siever and Davis (2004) that patients with schizotypal disorder would have volume deficits in the medial temporal lobe but limited abnormalities in the prefrontal cortex, whereas patients with schizophrenia would show volume reductions in the medial temporal lobe as well as in widespread regions of the prefrontal cortex.

Methods

Subjects

Twenty-five patients (15 males, 10 females) with schizotypal disorder, 53 patients with schizophrenia (32 males, 21 females) and 59 control subjects (35 males, 24 females) were included in this study. All subjects were right-handed. Demographic and clinical data of the subjects are presented in Table 1.

The patients with schizotypal disorder were recruited from among the subjects who visited the clinics of the Department of Neuropsychiatry, Toyama Medical and Pharmaceutical University Hospital manifesting schizotypal features with distress or associated problems in their lives. Structured clinical interviews were performed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen *et al.*, 1992) and Structured Clinical Interview for DSM-IV axis II disorders (SCID-II) (First *et al.*, 1997). They all met the criteria for schizotypal disorder in the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization, 1993) as well as the criteria for schizotypal personality disorder in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994). Based on the data from the CASH and SCID-II, subjects were diagnosed by a consensus of at least two experienced psychiatrists, and when necessary the propriety of including cases in the study was discussed among clinical staff members involved. None of the subjects was judged to meet the criteria for schizophrenia of ICD-10 or of DSM-IV currently or previously. At the time of MRI scanning, six patients were neuroleptic-naive and 19 patients were being treated with low doses of antipsychotics; six patients were being treated with typical neuroleptics and 13 patients were receiving atypical neuroleptics. All subjects have received consistent clinical follow-up and none of them has developed overt schizophrenia to date (mean follow-up period after MRI scanning = 2.5 years, SD = 1.9). Four of the 25 patients with schizotypal disorder were relatives of individuals with schizophrenia. Since schizotypal subjects rarely present themselves for clinical care, our clinic-based sample was considered to be somewhat more severely ill than may be expected of schizotypal individuals among the general population.

The patients with schizophrenia were diagnosed based on the CASH and Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (First *et al.*, 1996). They fulfilled both ICD-10 and DSM-IV criteria for schizophrenia. All schizophrenia patients apart from one female patient were receiving neuroleptic medication; 25 patients were being treated with typical neuroleptics and 27 patients were receiving atypical neuroleptics. The clinical status of the schizophrenia patients was variable; some of them were in an active psychotic episode and others were in partial remission or in a residual phase. All patients with schizotypal disorder and schizophrenia were physically healthy and none had a history of head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. Clinical symptoms were rated by well-trained psychiatrists or psychologist within 1 month of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Inter-rater intraclass correlation coefficients were over 0.92 for all the subscale scores and the total scores of the SANS and the SAPS.

The control subjects consisted of healthy volunteers recruited from among the community and hospital staff or were medical and pharmaceutical students. They were interviewed by psychiatrists using the questionnaire concerning their family and past histories, and present illness. Subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorder. They were also screened for a history of psychiatric disorders in their first-degree relatives. All control subjects were given the Minnesota Multiphasic Personality Inventory, and subjects were excluded if they had abnormal profiles with any T-score exceeding 70. The three groups were matched for age, sex, handedness, height and parental education (Table 1).

After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the

Table 1 Demographic and clinical characteristics of patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

	Schizotypal disorder patients (n = 25)	Schizophrenia patients (n = 53)	Healthy comparison subjects (n = 59)
Male/female	15/10	32/21	35/24
Handedness	25 right	53 right	59 right
Age (years)	25.5 ± 5.7	25.3 ± 5.0	24.3 ± 5.3
Height (cm)	164.6 ± 8.7	166.1 ± 7.3	167.0 ± 7.3
Weight (kg)	60.3 ± 9.7	61.7 ± 12.7	58.1 ± 9.4
Education (years)	13.5 ± 1.8†	13.2 ± 1.9†	16.0 ± 2.5
Parental education (years)	12.1 ± 1.9	12.2 ± 2.1	12.8 ± 2.4
Age at onset (years)	–	21.7 ± 4.5	–
Duration of illness (years)	–	3.7 ± 3.8	–
Total SAPS score	16.0 ± 8.5	24.1 ± 20.5	–
Total SANS score	46.8 ± 24.5	45.7 ± 22.5	–
Drug dose (mg/day, haloperidol equivalent)*	3.9 ± 4.7	11.6 ± 9.4‡	–
Duration of medication (years)	0.3 ± 0.4	2.7 ± 3.1‡	–

Values represent mean ± SD. *Neuroleptic dosages of different classes of antipsychotic drugs were converted into haloperidol equivalents using the guideline by Toru (2001). *Post hoc* comparisons following analysis of variance (ANOVA) revealed: †$P < 0.01$, smaller than in controls; ‡$P < 0.01$, larger than in schizotypal disorder patients. SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms.

Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

There are considerable overlaps between the subjects in the present study and those in previous MRI studies from our group. Of the 25 patients with schizotypal disorder, 15 and 17 patients overlapped with those in the volumetric MRI studies of the anterior cingulate gyrus (Takahashi *et al.*, 2002*b*, 2004) and of the internal capsule (Suzuki *et al.*, 2004), respectively. Of the 53 patients with schizophrenia, 34 overlapped with those in the volumetric MRI studies (Takahashi *et al.*, 2002*a*; Zhou *et al.*, 2003; Niu *et al.*, 2004). In the VBM study by Kawasaki *et al.* (2004), 17 schizotypal patients and 20 schizophrenia patients were the same as those in the present study. In these previous studies, 37–54 of the control subjects also overlapped with those in the present study according to the stages of our research.

MRI acquisition and processing

MRI scans were acquired with a 1.5 T scanner (Vision; Siemens Medical System, Erlangen, Germany). A three-dimensional T1-weighted gradient-echo sequence FLASH (fast low-angle shots) with 1 × 1 × 1 mm voxels was used. Imaging parameters were: TE (echo time) = 5 ms; TR (repetition time) = 24 ms; flip angle = 40°; field of view = 256 mm; matrix size = 256 × 256.

Image processing for volumetric ROI analysis has been described in detail previously (Takahashi *et al.*, 2002*a*). Briefly, on a Unix workstation (Silicon Graphics, Mountain View, CA, USA), the image data were processed with the software package Dr View 5.0 (Asahi Kasei Joho System, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into entire contiguous coronal slices of 1 mm thickness perpendicular to the anterior commissure–posterior commissure line. The whole cerebrum was separated from the brainstem and cerebellum. The signal intensity histogram distributions across the whole cerebrum were used to segment the voxels semiautomatically into grey matter, white matter and cerebrospinal fluid (CSF). Using the thresholds between the tissue compartments, volumes of whole hemispheric grey matter and white matter were calculated. These whole hemispheric grey matter and white matter volumes summed to the whole cerebral hemisphere volume, which did not include CSF or ventricles. Intracranial volume (ICV) was measured by manual tracing of the intracranial cavity on reformatted 5 mm thick sagittal slices as described previously (Zhou *et al.*, 2003).

Volumetric analysis of ROIs

The ROIs for volumetric measurements were placed on the medial temporal structures and prefrontal cortex, as presented in Figs 1 and 2, respectively.

Medial temporal lobe

The amygdala, hippocampus and parahippocampal gyrus were manually outlined on consecutive coronal 1 mm slices with the corresponding sagittal and axial planes simultaneously presented for reference. Volumes of grey and white matter in each of these structures were measured together. The detailed procedures for delineation of these structures were described previously (Niu

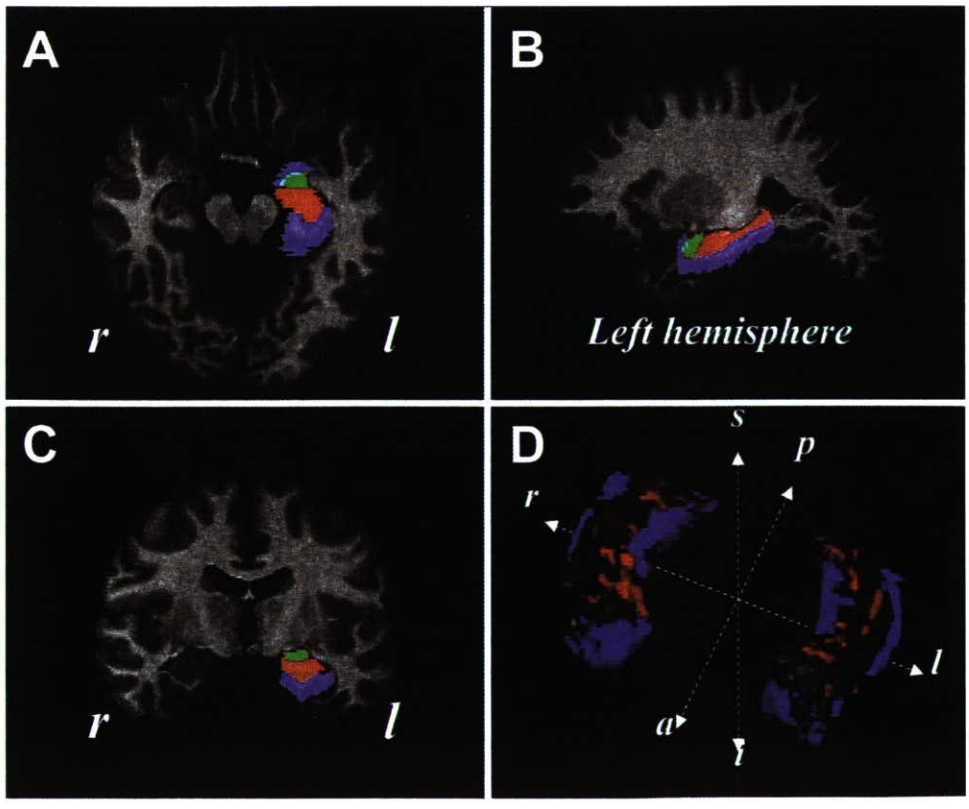

Fig. 1 Delineations of medial temporal regions of interest taken from mutually orthogonal transaxial (**A**), sagittal (**B**) and coronal (**C**) planes. A three-dimensional reconstructed image of the three regions is also shown (**D**). Each of the regions is differentially coloured: amygdala (green), hippocampus (red) and parahippocampal gyrus (blue). a, anterior; i, inferior; l, left; p, posterior; r, right; s, superior.

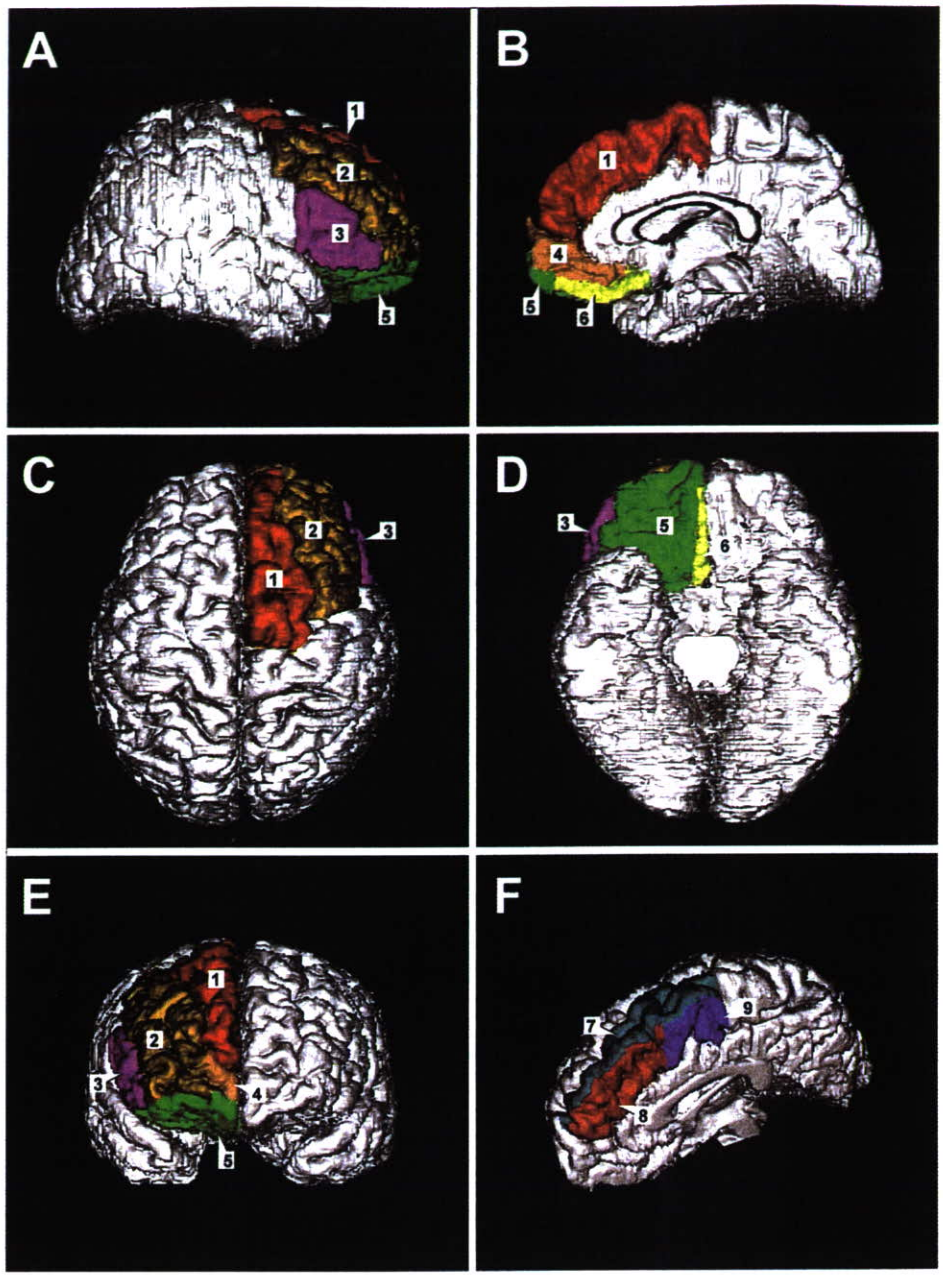

Fig. 2 Three-dimensional reconstructed images of prefrontal regions of interest presenting right lateral (**A**), right medial (**B**), dorsal (**C**), ventral (**D**) and anterior (**E**) views of the brain. Panel **F** demonstrates subdivisions of superior frontal gyrus. 1, superior frontal gyrus; 2, middle frontal gyrus; 3, inferior frontal gyrus; 4, ventral medial prefrontal cortex; 5, orbitofrontal cortex; 6, straight gyrus; 7, dorsolateral part of superior frontal gyrus; 8, dorsal medial prefrontal cortex; 9, supplementary motor cortex.

et al., 2004; Suzuki *et al.*, 2005*a*). The inferior border of the amygdala in contact with the hippocampal head was determined by reference to the sagittal plane since the boundary between the hippocampus and the amygdala is more readily identified on the sagittal plane (Convit *et al.*, 1999). Anatomical boundaries for these structures are presented in Table 2.

Prefrontal cortex

Delineation of the prefrontal cortex was partially based on the works of Rademacher *et al.* (1992) and Crespo-Facorro *et al.* (1999*a*). Parcellation of the frontal lobe into subcomponents was performed according to the anatomical landmarks that were, in principle, intrinsic to the brain (sulci/gyri). With the availability of synchronous–orthogonal views in three dimensions in conjunction with the context of gyri/sulci on successive slices, decisions about the landmarks could be made readily. First, the whole frontal lobe was separated from the rest of the brain by the central sulcus. The prefrontal area was demarcated by subtracting the precentral gyrus and the cingulate gyrus from the whole frontal lobe. By this definition of the prefrontal area, it inevitably includes the premotor cortex [Brodmann area (BA) 6 and part of BA 8]. The paracingulate gyrus (approximately corresponding to BA 32), when present, was included in the prefrontal area. After the extraction of the prefrontal

Table 2 Anatomical landmarks demarcating the regions of interest

Region	Anatomical landmark
Medial temporal region	
Amygdala	
Anterior border	Appearance of oval-shaped grey matter of the amygdala
Posterior border	Thin strip of grey matter of the hippocampal–amygdala transitional area
Superior border	Cerebrospinal fluid overlying the semilunar gyrus and its medial extension
Inferior border	Alveus
Lateral border	Temporal lobe white matter and extension of the temporal horn
Medial border	Thin strip of parahippocampal white matter (angular bundle)
Hippocampus	
Anterior border	Alveus
Posterior border	Level of the last appearance of fibres of the fornix
Superior border	Alveus
Inferior border	White matter of parahippocampal gyrus
Lateral border	Inferior horn of lateral ventricle
Medial border	Mesial edge of temporal lobe
Parahippocampal gyrus	
Anterior border	Level of the first appearance of the temporal stem
Posterior border	Level of the last appearance of fibres of the fornix
Superior border	Inferior grey border of the hippocampal formation
Lateral border	A line drawn from the most lateral border of the hippocampal flexure to the collateral sulcus
Prefrontal area	
Superior frontal gyrus (includes the paracingulate gyrus when it exists)	
Lateral inferior border	Superior frontal sulcus
Medial inferior border	Cingulate sulcus and, in the most anterior part, superior rostral sulcus
Anterior border	Frontomarginal sulcus, which extends from superior frontal sulcus
Posterior border	Precentral sulcus on the lateral surface and paracentral sulcus on the medial surface
Dorsolateral part	Medially separated by the superior margin of the hemisphere
Medial part	Dorsolaterally separated by the superior margin of the hemisphere
Dorsal medial prefrontal cortex	Posteriorly demarcated by the coronal plane through the most anterior tip of the inner surface of the genu of the corpus callosum
Supplementary motor area	Anteriorly demarcated by the same coronal plane as above
Middle frontal gyrus	
Superior border	Superior frontal sulcus
Inferior border	Inferior frontal sulcus
Anterior border	Frontomarginal sulcus, which extends from superior frontal sulcus
Posterior border	Precentral sulcus
Inferior frontal gyrus	
Superior border	Inferior frontal sulcus
Inferior border	Frontomarginal sulcus or lateral orbital sulcus in the anterior part and superior circular sulcus in the operculum
Anterior border	Frontomarginal sulcus, which extends from inferior frontal sulcus
Posterior border	Precentral sulcus
Ventral medial prefrontal cortex	
Superior border	Superior rostral sulcus in the anterior part and cingulate sulcus in the posterior part
Inferior border	Inferior rostral sulcus (the lowest visible sulcus in the medial surface of the hemisphere)
Anterior border	Frontomarginal sulcus, which extends from superior rostral sulcus
Posterior border	More posterior coronal plane through either of posterior extreme of cingulate sulcus or superior rostral sulcus
Orbitofrontal cortex	
Anterior/lateral border	Frontomarginal sulcus in the anterior part, lateral orbital sulcus in the intermediate part and inferior circular sulcus in the posterior part
Medial border	Superior rostral sulcus, which anteriorly merges into frontomarginal sulcus in the rostral part and olfactory sulcus on the ventral surface of the hemisphere
Posterior border	The most posterior coronal plane containing medial orbital gyrus
Straight gyrus	
Lateral border	Olfactory sulcus
Medial border	Inferior rostral sulcus (the lowest visible sulcus in the medial surface of the hemisphere)
Anterior border	Anterior extreme of olfactory sulcus
Posterior border	Olfactory trigone

area, it was subdivided into six subregions: the superior frontal gyrus, which was further subdivided into three parts (dorsolateral part, dorsal medial prefrontal cortex and supplementary motor cortex); middle frontal gyrus; inferior frontal gyrus; ventral medial prefrontal cortex; orbitofrontal cortex; and straight gyrus. Anatomical boundaries for each region are described in Table 2. All the volumetric measurements were performed on reformatted consecutive 1 mm coronal slices by manual outlining. Grey matter volumes of the regional cortices were calculated by applying the segmentation procedure described previously.

Three trained raters (S.Z., H.H. and L.N.), who were blinded to the subjects' identities, measured the volumes of the prefrontal regions, the amygdala, and the hippocampus and parahippocampal gyrus, respectively. Inter- and intra-rater intraclass correlation coefficients in five randomly selected brains were over 0.92 for the prefrontal ROIs and over 0.93 for the medial temporal ROIs.

Statistical analysis

Statistical differences in the regional volume measures were analysed by repeated measures multivariate analysis of covariance (MANCOVA) with ICV and age as covariates for each region, with diagnosis group (schizophrenia patients, schizotypal disorder patients, control subjects) and gender (male, female) as between-subject factors and hemisphere (right, left) as a within-subject factor. For the comparison of ICV, only age was treated as a covariate. *Post hoc* Tukey's tests were employed to follow up the significant main effects or interactions yielded by MANCOVAs. Pearson's partial correlation coefficients, controlling for ICV and age, were calculated to examine relationships between the ROI volumes and the clinical variables. Statistical significance was defined as $P < 0.05$ (two-tailed). To prevent a possible type I error due to multiple tests, a Bonferroni correction was applied for correlation analyses.

Results

Volumes of measured ROIs and results of MANCOVAs for the main effect of diagnosis are presented in Tables 3, 4 and 5. We report below the results concerning main effects of diagnosis or interactions involving diagnosis only when

Table 3 Volumes of intracranial cavity, cerebral hemisphere and cerebral grey and white matter in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	df	*P*
Intracranial volume	1526 ± 150	1496 ± 155	1509 ± 128	0.71	2,130	0.492
Whole cerebral hemisphere				1.84	2,129	0.162
Left[§]	559.0 ± 56.6	538.6 ± 59.5	553.8 ± 48.8			
Right	566.1 ± 57.2	545.8 ± 60.4	561.3 ± 49.2			
Whole cerebral grey matter				4.89	2,129	0.008
Left[#]	362.1 ± 40.5	339.8 ± 39.3[†,‡]	356.4 ± 36.2			
Right	353.6 ± 40.3	329.9 ± 37.5[†,‡]	347.6 ± 35.6			
Whole cerebral white matter				1.69	2,129	0.187
Left[§]	197.0 ± 26.3	198.8 ± 33.1	197.3 ± 31.5			
Right	212.5 ± 29.3	215.9 ± 39.4	213.7 ± 36.0			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [†]$P < 0.01$, smaller than in controls; [‡]$P < 0.01$, smaller than in schizotypal disorder patients; [§]$P < 0.01$, smaller than on right hemisphere; [#]$P < 0.01$, larger than on right hemisphere.

Table 4 Volumes of medial temporal lobe structures in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	df	*P*
Amygdala				19.08	2,129	<0.001
Left[§]	0.96 ± 0.13[†]	0.99 ± 0.15[†]	1.13 ± 0.14			
Right	0.97 ± 0.15[†]	1.05 ± 0.17[†]	1.15 ± 0.14			
Hippocampus				3.24	2,129	0.042
Left[§]	2.83 ± 0.37[‡]	2.89 ± 0.42[†]	3.04 ± 0.40			
Right	3.03 ± 0.39[‡]	3.09 ± 0.56[†]	3.24 ± 0.35			
Parahippocampal gyrus				0.34	2,129	0.706
Left	7.22 ± 0.73	7.01 ± 1.13	7.15 ± 0.90			
Right	7.22 ± 0.57	7.09 ± 1.08	7.31 ± 0.76			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [†]$P < 0.01$, [‡]$P < 0.05$, smaller than in controls; [§]$P < 0.01$, smaller than on right hemisphere.

Table 5 Volumes of whole prefrontal grey and white matter and prefrontal cortex subcomponents in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects

Regions of interest	Schizotypal disorder patients	Schizophrenia patients	Healthy comparison subjects	Diagnosis effect		
				F	*df*	*p*
Prefrontal grey matter				3.51	2,129	0.032
Left[‡‡]	97.18 ± 13.65	91.05 ± 12.32[†,§]	96.38 ± 9.88			
Right	94.99 ± 13.33[††]	88.16 ± 11.82[†,§]	92.38 ± 9.54			
Prefrontal white matter				1.34	2,129	0.264
Left[§§]	46.72 ± 7.07	44.54 ± 8.69	47.13 ± 7.66			
Right	49.73 ± 7.26	49.14 ± 10.05	50.28 ± 9.05			
Superior frontal gyrus				3.49	2,129	0.033
Left[‡‡]	28.91 ± 5.31	27.49 ± 4.21[†]	29.64 ± 4.05			
Right	27.65 ± 5.29	25.63 ± 4.37[†,#]	27.76 ± 3.95			
Dorsolateral part				0.53	2,129	0.589
Left[‡‡]	12.42 ± 3.19	12.34 ± 2.33	13.02 ± 2.81			
Right	12.27 ± 3.46	11.76 ± 2.83	12.34 ± 2.33			
Dorsal medial prefrontal cortex				4.84	2,129	0.009
Left[‡‡]	10.19 ± 2.35	9.16 ± 1.99[†,#]	10.16 ± 1.81			
Right	9.39 ± 1.92	8.72 ± 1.77[†]	9.73 ± 1.79			
Supplementary motor cortex				3.48	2,129	0.033
Left[‡‡]	6.30 ± 1.09	6.00 ± 1.00[‡]	6.47 ± 1.19			
Right	5.99 ± 1.56	5.14 ± 1.07[‡,#]	5.69 ± 1.23			
Middle frontal gyrus				2.90	2,129	0.058
Left[‡‡]	29.34 ± 5.67[††]	25.87 ± 4.95[†,§]	27.31 ± 4.62			
Right	28.44 ± 5.66[††]	25.50 ± 4.41[§]	26.53 ± 4.78			
Inferior frontal gyrus				4.92	2,129	0.008
Left[‡‡]	13.02 ± 2.65	12.58 ± 2.14[†]	13.87 ± 2.10			
Right	13.18 ± 2.22	12.05 ± 2.19[†,§]	12.89 ± 1.83			
Ventral medial prefrontal cortex				0.92	2,129	0.397
Left	5.61 ± 1.22	5.51 ± 1.21	5.84 ± 1.12			
Right	5.56 ± 1.03	5.48 ± 1.17	5.69 ± 1.23			
Orbitofrontal cortex				0.47	2,129	0.622
Left	15.69 ± 1.91	15.11 ± 2.03	15.44 ± 1.57			
Right	15.58 ± 1.87	15.07 ± 2.07	15.47 ± 1.45			
Straight gyrus				15.45	2,129	<0.001
Left	3.06 ± 0.49	2.89 ± 0.45[†]	3.31 ± 0.49			
Right	3.02 ± 0.51[‡]	2.92 ± 0.43[†]	3.31 ± 0.50			

Values represent mean ± SD of measured volume (cm^3). *Post hoc* comparisons following multivariate analysis of variance with age and intracranial volume as covariates (MANCOVA) revealed: [†]$P < 0.01$; [‡]$P < 0.05$, smaller than in controls; [§]$P < 0.01$, [#]$P < 0.05$, smaller than in schizotypal disorder patients; [††]$P < 0.05$, larger than in controls; [‡‡]$P < 0.01$, larger than on right hemisphere; [§§]$P < 0.01$, smaller than on right hemisphere.

they were significant or had a nearly significant trend, and subsequent *post hoc* analyses.

Volumes of global brain structures

There were no significant differences in the volumes of intracranial cavity, whole cerebral hemisphere or whole cerebral white matter among diagnostic groups (Table 3). MANCOVAs revealed a significant main effect of diagnosis for the whole cerebral grey matter (Table 3). The volumes of whole cerebral grey matter were significantly smaller in the schizophrenia patients compared with the controls (*post hoc* tests, $P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for both hemispheres).

Volumes of medial temporal lobe

A significant main effect of diagnosis in MANCOVA was revealed in the amygdala and the hippocampus (Table 4). *Post hoc* analyses demonstrated that, compared with the controls, the volume of the amygdala was significantly smaller in the patients with schizotypal disorder ($P < 0.001$ for both hemispheres) and schizophrenia ($P < 0.001$ for both hemispheres). The volume of the hippocampus was also significantly smaller in the patients with schizotypal disorder ($P = 0.039$ for the left and $P = 0.020$ for the right) and schizophrenia ($P = 0.009$ for the left and $P = 0.005$ for the right) than in the controls. There was no significant difference in the amygdala or hippocampus volume between schizotypal disorder and schizophrenia. The parahippocampal gyrus measures did not differ among diagnostic groups (Table 4).

Volumes of prefrontal cortex

A significant main effect of diagnosis in MANCOVA was observed in the total prefrontal grey matter but not in the total prefrontal white matter (Table 5). *Post hoc* analyses

demonstrated that the prefrontal grey matter volume was significantly smaller in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for both hemispheres). In contrast, the schizotypal disorder patients had larger prefrontal grey matter than the controls in the right hemisphere ($P = 0.040$).

Among the prefrontal cortex subcomponents, MANCOVA revealed a significant main effect of diagnosis in the superior frontal gyrus, inferior frontal gyrus and straight gyrus, and an insignificant trend for main effect of diagnosis in the middle frontal gyrus (Table 5). When the superior frontal gyrus was further subdivided, a significant main effect of diagnosis was found only in the medial parts, such as the dorsal medial prefrontal cortex and supplementary motor cortex (Table 5). A significant interaction between diagnosis and gender was observed only in the inferior frontal gyrus [$F(2,129) = 3.97$, $P = 0.021$].

Post hoc analyses demonstrated that the superior frontal gyrus grey matter volume was significantly reduced in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P = 0.014$ for the right) (Fig. 3A). In the superior frontal gyrus subdivisions, the schizophrenia patients had a significantly

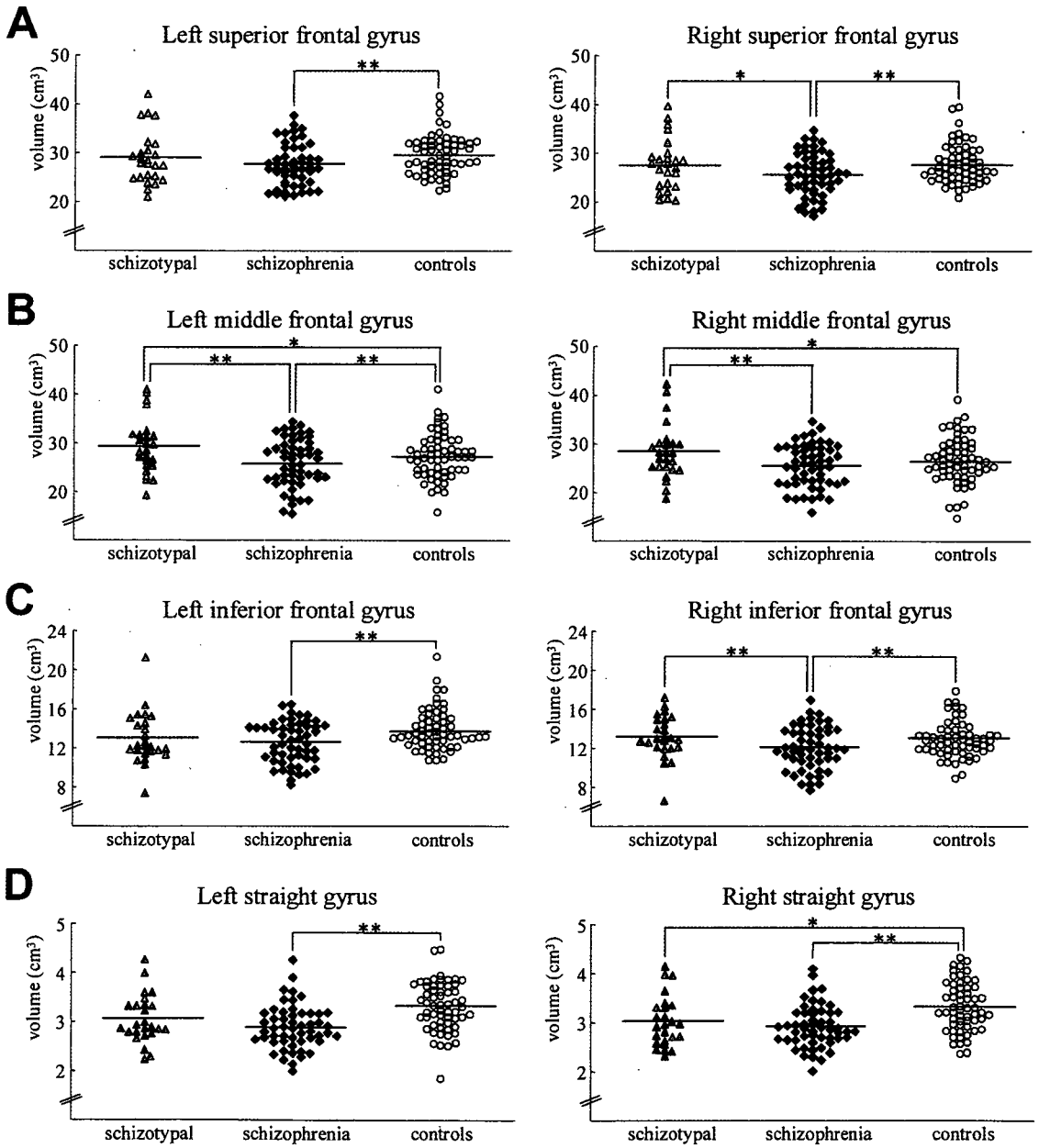

Fig. 3 Scatter plots of absolute volumes of grey matter for each prefrontal subcomponent in patients with schizotypal disorder, patients with schizophrenia and healthy comparison subjects: superior frontal gyrus (**A**), middle frontal gyrus (**B**), inferior frontal gyrus (**C**) and straight gyrus (**D**). Horizontal bars indicate means of each group. *$P < 0.05$; **$P < 0.01$: *post hoc* comparisons followed multivariate analysis of variance with age and intracranial volume as covariates.

smaller dorsal medial prefrontal cortex volume than the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P = 0.016$ for the left). The supplementary motor cortex volume in the schizophrenia patients was also significantly smaller than in the controls ($P = 0.022$ for the left and $P = 0.026$ for the right) and the schizotypal patients ($P = 0.013$ for the right).

The middle frontal gyrus volume was significantly smaller in the schizophrenia patients compared with the controls ($P = 0.002$ for the left) and the schizotypal patients ($P < 0.001$ for both hemisphere) (Fig. 3B). Further, the schizotypal patients had significantly larger middle frontal gyrus volume than the controls ($P = 0.026$ for both hemispheres) (Fig. 3B).

The inferior frontal gyrus volume was significantly reduced in the schizophrenia patients compared with the controls ($P < 0.001$ for both hemispheres) and the schizotypal patients ($P < 0.001$ for the right) (Fig. 3C). As a significant diagnosis × gender interaction was also found, we made *post hoc* comparisons separately in each gender. In the male subjects, significant volume reductions of the left inferior frontal gyrus were found in the patients with schizotypal disorder ($P = 0.001$) and schizophrenia ($P = 0.020$) compared with the controls. The female patients with schizophrenia had a significantly smaller volume than the patients with schizotypal disorder ($P < 0.001$ for both hemispheres) and the controls ($P < 0.001$ for the left and $P = 0.001$ for the right).

Compared with the controls, the straight gyrus volume was significantly smaller in the patients with schizotypal disorder ($P = 0.037$ for the right) and schizophrenia ($P < 0.001$ for both hemispheres) (Fig. 3D).

Correlations between volume measures and clinical variables

Partial correlation analyses controlling for ICV and age did not reveal any significant correlation between the volume measures of each ROI and daily dosage of neuroleptic medication or duration of medication in either the schizotypal disorder or the schizophrenia group. In addition, the volume measures were not significantly correlated with age at onset of illness or duration of illness in the schizophrenia patients.

To test the possibility that increases in the prefrontal cortex volumes in the schizotypal group reflect the compensatory mechanism secondary to the medial temporal lobe abnormalities, partial correlation coefficients were calculated between the volume of the right prefrontal grey matter or the bilateral middle frontal gyri and the volume of the amygdala or the hippocampus. The right hippocampal volume was significantly correlated with the right prefrontal grey matter volume ($r = -0.620$, $P = 0.002$) and the left middle frontal gyrus volume ($r = -0.607$, $P = 0.002$) even after Bonferroni correction ($P < 0.004$).

Discussion

There are two main points in this study: (i) volumes of the amygdala and the hippocampus were commonly reduced in patients with schizophrenia and schizotypal disorder; (ii) volumes of the subcomponents of the prefrontal cortex were widely reduced in schizophrenia patients, whereas those in schizotypal subjects were mostly preserved.

Temporolimbic pathology as vulnerability

Consistent with the previous VBM study (Kawasaki *et al.*, 2004), the present results suggest that the volume reduction of the amygdala and hippocampus is a common morphological basis for the schizophrenia spectrum. Studies of family members of patients with schizophrenia have also revealed evidence of medial temporal abnormalities similar to those found in schizophrenia patients (Lawrie *et al.*, 1999; Seidman *et al.*, 1999, 2002; Van Erp *et al.*, 2002). Schizotypal disorder has dual aspects that are contradictory in relation to the liability to schizophrenia. Schizotypal subjects are generally spared overt psychosis in spite of the presence of incipient psychotic symptoms. On the other hand, they have a higher incidence of developing schizophrenia than the general population (Fenton and McGlashan, 1989). Thus they are assumed to have vulnerability to schizophrenia but are simultaneously protected from developing full-blown psychosis. Our findings support the notion that reduced temporolimbic volume represents a vulnerability marker, which is necessary but not sufficient for developing schizophrenia (Seidman *et al.*, 2002; Kurachi, 2003*a*, *b*).

Prefrontal involvement in schizophrenia

There seems general agreement that total prefrontal grey matter is reduced in patients with schizophrenia compared with healthy subjects (Shenton *et al.*, 2001; Selemon *et al.*, 2002). However, findings in previous studies that have parcellated the prefrontal cortex into subcomponents have varied in spatial distribution of the gross anatomical changes within the prefrontal cortex in schizophrenia (Buchanan *et al.*, 1998, 2004; Baaré *et al.*, 1999; Goldstein *et al.*, 1999; Crespo-Facorro *et al.*, 2000; Gur *et al.*, 2000; Sanfilipo *et al.*, 2000; Convit *et al.*, 2001; Yamasue *et al.*, 2004). These inconsistencies may be due, in large part, to the use of different image measurement procedures. In particular, there has been substantial variability among studies in definitions of boundaries subdividing the prefrontal cortex into subcomponents.

The present study demarcated the prefrontal ROIs by fully taking account of the anatomical landmarks intrinsic to the frontal lobe, and revealed widespread alterations in volume of the prefrontal cortex in schizophrenia. This is consistent with the observation that schizophrenia patients have deficits in extensive neurobehavioural domains involving the prefrontal cortex, such as cognition including executive functions, motivation and emotion (Goldman-Rakic and Selemon, 1997).

The present study also suggested a considerable preference for anatomical involvement of the prefrontal cortex in schizophrenia. When the superior frontal gyrus was subdivided into dorsolateral and medial parts, significant volume reduction

was observed only in the medial part. This finding should be interpreted with caution because the corpus callosum, which has been reported to be abnormal in schizophrenia (Shenton *et al.*, 2001), was used as a landmark to define the subregions of the medial part of the superior frontal gyrus. Thus, the volume differences found may reflect differences in shape or volume of the corpus callosum between groups. However, decreased blood flow in the medial prefrontal region has been shown in schizophrenia patients during the performance of memory tasks (Andreasen *et al.*, 1996; Crespo-Facorro *et al.*, 1999*b*). Moreover, functional neuroimaging studies have demonstrated that the medial prefrontal cortex, including the paracingulate cortex, is activated by tasks involving autonomic arousal, many forms of self-monitoring and social cognition (Gallagher and Frith, 2003; Ridderinkhof *et al.*, 2004). The possible relevance of medial prefrontal dysfunction to the pathophysiology of schizophrenia seems worthy of examination in future studies.

Prefrontal involvement in schizotypal disorder

To our knowledge, this study is the first to report comprehensive volumetric results of the prefrontal cortex subcomponents in schizotypal subjects. In all parts except the right straight gyrus, prefrontal cortical volumes in the schizotypal patients were not reduced, while the bilateral middle frontal gyrus and right prefrontal grey matter as a whole were even larger than those of the control subjects. These findings support the model proposed by Siever and Davis (2004) and provide more compelling morphological evidence for their predictions. Preserved volume of the prefrontal cortical regions is consistent with the findings that performance in tasks involving the frontal lobe functions is better in schizotypal individuals than that in patients with schizophrenia (Mitropoulou *et al.*, 2002; Matsui *et al.*, 2004). Increases in the prefrontal grey matter volume might reflect functional compensation, which a few functional brain imaging studies have suggested to occur in the prefrontal cortex of schizotypal subjects (Buchsbaum *et al.*, 1997, 2002). The possible compensatory mechanism will be discussed further below.

Prefrontal pathology and manifestation of psychosis

Differential involvement of the prefrontal cortex between patients with schizophrenia and schizotypal disorder in the present study strongly suggests that prefrontal pathology is critical for overt manifestation of psychosis in schizophrenia spectrum patients. Previous literature on MRI, however, has highlighted several non-frontal regions involving the positive psychotic symptoms in schizophrenia. In particular, volume loss in the superior temporal gyrus has been related to a variety of psychotic symptoms (Barta *et al.*, 1990; Shenton *et al.*, 1992; Menon *et al.*, 1995; Kim *et al.*, 2003). Other studies revealed an inverse relationship between the amygdala–hippocampal complex and overall positive symptoms (Bogerts *et al.*, 1993) or between the paralimbic cortices and Schneiderian symptoms (Suzuki *et al.*, 2005*b*). It may be notable that volume reduction of the superior temporal gyrus was reported commonly in schizotypal subjects (Dickey *et al.*, 1999, 2002*b*; Kawasaki *et al.*, 2004) and patients with schizophrenia (Shenton *et al.*, 2001).

The prefrontal cortex has a high density of interconnections with almost all other sectors of the cerebral cortex, including the limbic areas. One of the integrative functions of the prefrontal cortex, through these widespread connections, is thought to be the inhibitory control of interference (Fuster, 1997; Mesulam, 2000). It probably protects the structure of behaviour or thought from external or internal interfering influences. From our results, as has been suggested in previous literature (Frith *et al.*, 2000; Kurachi, 2003*b*), it might be possible to imply that deficits in the inhibitory function of the prefrontal cortex result in emergence of prominent psychotic symptoms, which might have a source in the dysfunctional medial and/or lateral temporal regions.

A few functional brain imaging studies have provided supporting evidence for this notion that prefrontal cortex dysfunction is correlated with exaggerated subcortical dopaminergic transmission in schizophrenia (Bertolino *et al.*, 2000; Meyer-Lindenberg *et al.*, 2002). Animal studies have also shown that neonatal excitotoxic lesions of the medial temporal lobe lead to developmental abnormality of the prefrontal cortex (Bertolino *et al.*, 1997, 2002) in association with postpubertal emergence of excessive subcortical dopamine transmission (Lipska *et al.*, 1993; Saunders *et al.*, 1998; Uehara *et al.*, 2000). Any significant correlation between the prefrontal cortical volumes and positive psychotic symptoms in schizophrenia, if present, would support a possible critical role of the prefrontal cortex in the manifestation of overt psychosis. However, we could not examine the symptom–morphology relationships because our schizophrenia sample, with varying clinical status, was not suitable for such analysis. This should be noted as a limitation of the present study.

Taken the results together, however, it is tempting to speculate that some genetic or environmental factor, which enables the prefrontal cortex to compensate for the medial temporal lobe abnormality, e.g. increases in synapses secondary to reduced inputs from the medial temporal lobe, may contribute to avoiding prominent and persistent psychotic symptoms in schizotypal disorder. The significant negative correlations found between the prefrontal grey matter volume and the hippocampal volume in the schizotypal group may lend support to this view. It cannot be stated, however, that the prefrontal cortex is specifically involved in the compensatory mechanism, because the implications of the present study are limited by the lack of volume measures of other neocortical regions, such as the temporal neocortex and the parietal cortex, where morphological changes have also been reported in schizophrenia (Shenton *et al.*, 2001; Buchanan *et al.*, 2004).

Possible confounding factors

A few possible confounding factors in the present study must be taken into account. First, significant differences in the medication status between the schizophrenia and schizotypal groups might have affected the volumetric results. However, the dosage or duration of neuroleptic medication was not correlated with any of the volume measures of the medial temporal and prefrontal structures. Furthermore, sustained neuroleptic treatment could not easily explain the fact that the medial temporal volumes were comparably reduced both in the patients with schizophrenia and in those with schizotypal disorder. Secondly, in the present study young patients with schizotypal disorder were included for comparison with the schizophrenia patients with relatively short durations of illness and medication. This has made it difficult to eliminate the possibility of including schizotypal subjects who would develop overt schizophrenia later on. All the patients included have continued to receive prospective clinical follow-up.

Conclusions

Detailed volumetric comparisons of the medial temporal structures and the prefrontal cortex subcomponents revealed differential morphological alterations in these structures between the patients with schizotypal disorder and those with schizophrenia. Volume reductions in the amygdala and the hippocampus common to both patient groups may represent the vulnerability to schizophrenia, while prefrontal volume loss preferentially observed in schizophrenia may be a critical factor for overt manifestation of psychosis. Although the specificity of this relationship should further be clarified, possible differential contributions of prefrontal and temporolimbic pathologies to the mechanisms of psychosis provide a framework for further studies investigating the pathogenesis of schizophrenia.

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Morphological brain changes associated with Schneider's first-rank symptoms in schizophrenia: a MRI study

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ABSTRACT

Background. Schneider's first-rank symptoms involve an alienated feature of the sense of one's own mental or physical activity. To clarify the brain morphological basis for the production of these symptoms, volumes of the frontal and medial temporal regions and their clinical correlates were examined in patients with schizophrenia.

Method. Twenty-two patients with schizophrenia and 44 age- and gender-matched healthy control subjects were included. All patients were in their psychotic episodes with definite Schneiderian symptoms, rated by using the Scale for Assessment of Positive Symptoms. Volumetric measurements of high-resolution magnetic resonance imaging were performed in the prefrontal area, cingulate gyrus, and precentral gyrus, and the medial temporal structures such as the amygdala, hippocampus, and parahippocampal gyrus.

Results. Patients had significantly decreased volumes in the cingulate gray matter and the amygdala compared to controls. In the patient group, Schneiderian symptom severity showed significant inverse correlations with volumes of the right posterior cingulate gray matter and of the left anterior parahippocampal gyrus.

Conclusions. Schneiderian symptoms may be associated with morphological abnormalities in the limbic-paralimbic regions such as the cingulate gyrus and parahippocampal gyrus, which possibly serve the self-monitoring function and the coherent storage and reactivation of information.

INTRODUCTION

First-rank symptoms, identified by K. Schneider as a set of phenomena indicative of schizophrenia (Schneider, 1959), have played a critical role in concepts of schizophrenia, despite the lack of consistent empirical support for their diagnostic significance (Goldman *et al.* 1992; Peralta & Cuesta, 1999). Based on the analysis of symptom clusters in schizophrenia, these symptoms have been suggested to represent a clinical syndrome distinct from other types of positive psychotic symptoms (Gur *et al.* 1994; Yuasa *et al.* 1995). Although Schneider himself avoided speculating on the theoretical implications of these phenomena, it is notable that almost all of them involve an alienated feature of the sense of one's own mental or physical activity (Liddle, 2000; Kurachi, 2003*a*). A failure of the central monitoring system has been hypothesized for the explanation of these symptoms (Frith, 1987; Frith & Done, 1988), and this hypothesis has been supported by psychological evidence in studies of schizophrenia patients with such symptoms (Frith & Done, 1989; Mlakar *et al.* 1994; Keefe *et al.*

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1999; Brebion *et al.* 2000). It has been proposed that self-monitoring involves a network of areas linking the prefrontal cortex and the hippocampus via the parahippocampal gyrus and the cingulate cortex (Frith & Done, 1988; Gray *et al.* 1991).

With regard to the neuroanatomical regions involved in Schneiderian symptoms in schizophrenia, functional neuroimaging studies have suggested that auditory hallucinations are related to abnormalities in brain regions such as the left inferior frontal, temporal, and parahippocampal cortices (Friston *et al.* 1992; Liddle *et al.* 1992; Suzuki *et al.* 1993; McGuire *et al.* 1995; Silbersweig *et al.* 1995; Shergill *et al.* 2000). In our previous study (Yuasa *et al.* 1995), the severity of auditory hallucinations and disturbance of the self (designated as 'alienation' syndrome) were related to increased blood flow in the right parietal and inferior frontal regions. Schizophrenia patients predominantly with Schneiderian delusions and hallucinations were reported to have increased glucose metabolism in the mid-temporal region (Gur *et al.* 1995). Hyperactivation of the right inferior parietal lobule and cingulate gyrus was observed during voluntary movement in schizophrenia patients experiencing delusions of control (Spence *et al.* 1997). The severity of Schneiderian first-rank symptoms was correlated with increased blood flow in the right superior parietal cortex and decreased blood flow in the left posterior cingulate and lingual cortex (Franck *et al.* 2002). Frith *et al.* (2000) have speculated that, at the physiological level, the fundamental abnormality associated with delusions of control may be found in the system which generates an inhibitory signal, such as the prefrontal cortex and/or anterior cingulate cortex, and that a failure to suppress activity in the parietal cortex would lead to delusions of control, while a failure to suppress activity in the temporal cortex would lead to hallucinations or thought insertion.

Schizophrenia patients demonstrate subtle morphological abnormalities principally in fronto-temporo-limbic-paralimbic structures (Shenton *et al.* 2001; Suzuki *et al.* 2002). There have been several structural magnetic resonance imaging (MRI) studies of the volume changes in regions which take part in manifestation of the positive psychotic symptoms. Positive formal thought disorder has been shown to relate to volume loss in the left posterior superior temporal gyrus (Shenton *et al.* 1992; Menon *et al.* 1995; Vita *et al.* 1995; Rajarethinam *et al.* 2000). Auditory hallucinations have been related to the left anterior superior temporal gyrus (Barta *et al.* 1990; Levitan *et al.* 1999) and the insula (Shapleske *et al.* 2002). Other studies revealed an inverse relationship between delusions and the left superior temporal gyrus (Menon *et al.* 1995), or overall positive psychotic symptoms and the left superior temporal gyrus (Flaum *et al.* 1995; Kim *et al.* 2003), the insula (Crespo-Facorro *et al.* 2000) or the medial temporal structures (Bogerts *et al.* 1993). However, most of the studies cited did not specifically focus on the alienated feature of psychotic symptoms. In an earlier MRI study, patients with predominantly Schneiderian delusions and hallucinations were reported to have increased ventricle–brain ratios and reduced cranial and brain volumes (Gur *et al.* 1994), but subsequent studies failed to find the association between Schneiderian symptoms and frontal or temporal lobe volume (Turetsky *et al.* 1995; Cowell *et al.* 1996). Thus, the structural brain changes underlying Schneiderian symptoms and/or self-monitoring deficits in schizophrenia remain elusive.

In the present study, we employed high-resolution MRI and attempted to clarify the common morphological substrates of the schizophrenic syndrome characterized by an alienated feature. Only patients in active psychotic episodes with definite Schneiderian symptoms were included. We performed volumetric assessments of the frontal and medial temporal lobe structures. These MRI measures were compared to those of age- and gender-matched healthy comparison subjects, and, in the patient group, correlation analyses were conducted between volume measures and the severity of Schneiderian symptoms.

We hypothesized the following: (i) schizophrenia patients with Schneiderian symptoms would have volume deficits in frontal and medial temporal structures; and (ii) Schneiderian symptoms could be related to morphological abnormalities in components of a distributed network of prefronto-limbic-paralimbic structures, which have been implicated in the self-monitoring function.