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KEY WORD

精神 第4版

編集
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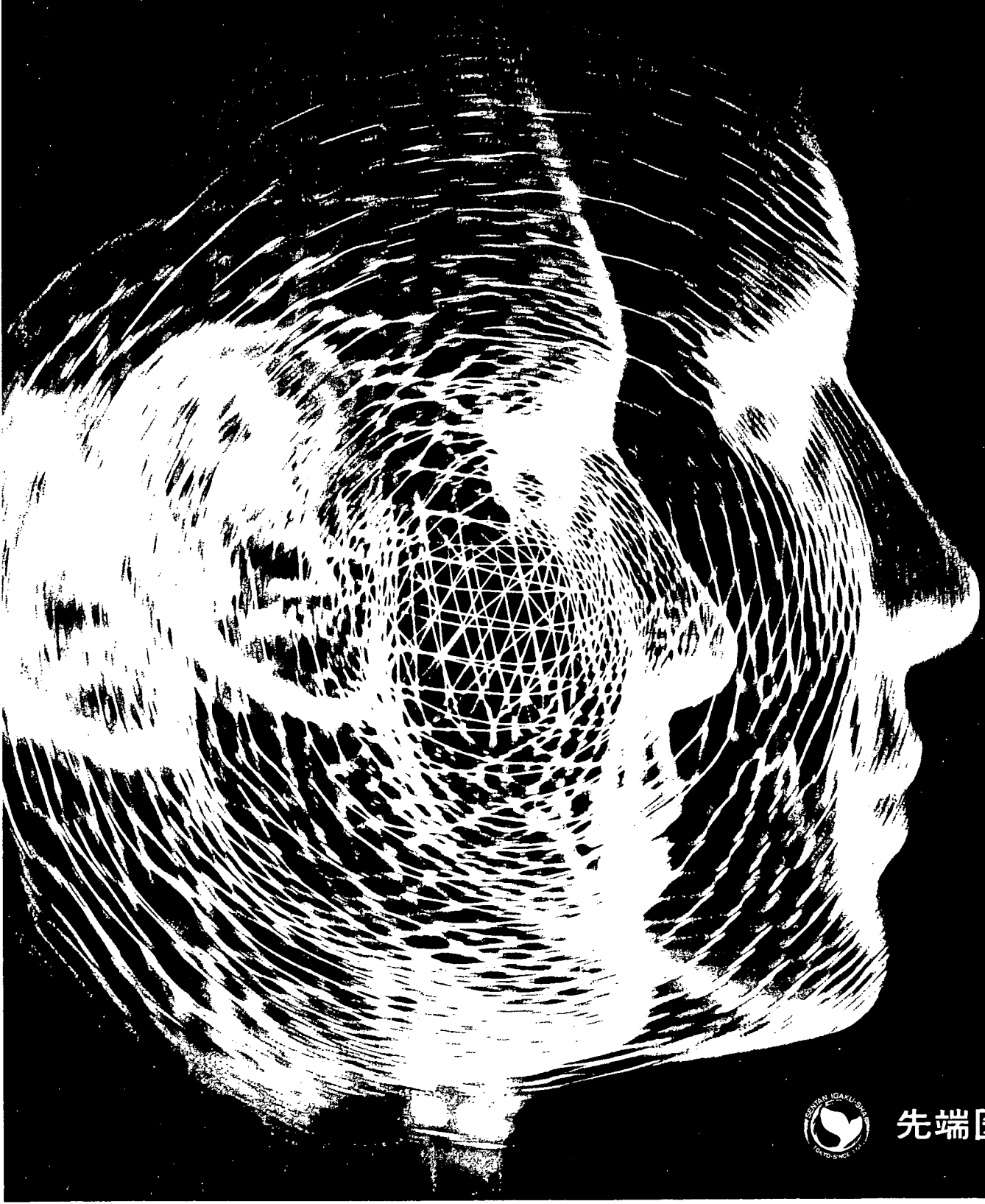
神庭重信
染矢俊幸
宮岡　等



先端医学社

ドパミンパーシャルアゴニスト

● **Dopamine partial agonist**

非定型抗精神病薬clozapineをモデルとして1990年代より開発が進められた一連の新規抗精神病薬は錐体外路系副作用が比較的少なく，それ以前の第1世代抗精神病薬と区別して第2世代抗精神病薬と総称されている．第2世代抗精神病薬も，第1世代抗精神病薬と同じくドパミンD_2受容体アンタゴニストであるが，第1世代のグループとはさらに異なる薬理学的基礎を有すると考えられている．たとえば，リスペリドン(risperidone)は，そのドパミンD_2受容体に対する親和性よりもセロトニン（5-HT)$_{2A}$受容体に対する親和性が相対的に高いことが臨床的な効果に寄与すると推測され，セロトニンドパミンアンタゴニスト（serotonin-dopamine antagonist：SDA）とよばれている．

これに対して，2006年にわが国で発売された新規抗精神病薬アリピプラゾール（aripiprazole）は，これまでの抗精神病薬とは薬理学的特徴がまったく異なり，ドパミンD_2受容体を部分的に活性化するパーシャルアゴニスト（partial agonist）として作用することから，ドパミンパーシャルアゴニスト（dopamine partial agonist：DPA）とよばれる．

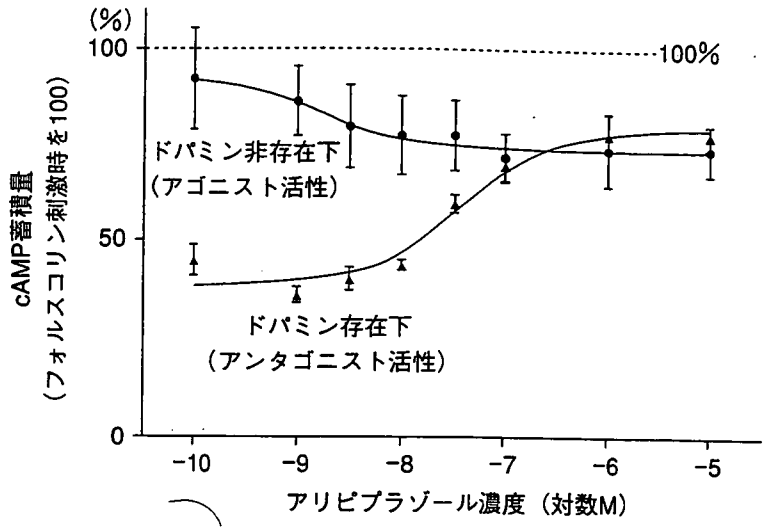
DPA型抗精神病薬の薬理作用

DPAは，ドパミンD_2受容体に対して高い親和性を有するが，その固有活性（intrinsic activity）はフルアゴニスト（full agonist）である内在性ドパミンよりも小さい．このことは，DPAはドパミンD_2受容体周辺の内在性ドパミンが過剰な状況では，ドパミンD_2受容体にアンタゴニストとしてはたらくことを意味している．一方，内在性ドパミンが乏しいと，アゴニストとしてはたらき，ドパミンD_2受容体を介する神経伝達を調整する．したがって，DPAはドパミン神経伝達を正常な状態に安定化させることからすぐれた抗精神病薬として期待される．

受容体結合実験において，ドパミンD_2受容体アゴニストは，G蛋白と共役した状態のドパミンD_2受容体に対してG蛋白非共役状態のドパミンD_2受容体とくらべてより高い親和性を有するが，アリピプラゾールは他のDPAとともに同様の性質を示す．また，ドパミンよりもドパミンD_2受容体に対する親和性（K_i値0.34 nM）がはるかに高い．組換え型ヒトドパミンD_2受容体を発現させたCHO細胞を用いた*in vitro*実験において，アリピプラゾールはドパミンによるドパミンD_2受容体刺激効果を，アリピプラゾールが単独で示す刺激効果の水準にまで戻す拮抗作用を示す（図❶）．さらに，ドパミン合成の律速酵素であるチロシン水酸化酵素活性を制御している前シナプス性ドパミンD_2自己受容体に作用してドパミン合成を抑制する．以上の基礎実験の結果は，アリピプラゾールがDPAとしての薬理作用を有することを示している．

健康成人にアリピプラゾールを14日間投与しPETを用いて脳内ドパミンD_2およびドパミンD_3受容体占拠率を測定した研究では，線条体におけるドパミンD_2受容体占拠率が90%を超えても錐体外路症状を認めなかったことから，同薬は従来の抗精神病薬と異なり線条体ドパミンD_2受容体に対してアンタゴニスト作用を示さないと考えられる．

アリピプラゾールは，ドパミンD_2受容体以外にドパミンD_3受容体，5-HT$_{1A}$および5-HT$_{2A}$受容体に対しても高い親和性（K_i値はそれぞれ0.8，1.7，3.4 nM）を有している[2]．とくに5-HT$_{1A}$受容体にはSDA型抗精神病薬と同じくパーシャル



図❶ ドパミンD_2受容体刺激応答に対するDPA型抗精神病薬アリピプラゾールの作用

CHO細胞に発現させたヒトドパミンD_2受容体をEEDQにより部分的に不活性化している．アリピプラゾールは，ドパミン非存在下ではフォルスコリンによるcAMP蓄積を部分的に抑制する（アゴニスト活性）．一方，ドパミン100 nM存在下ではドパミンのドパミンD_2受容体刺激によるcAMP蓄積抑制効果に拮抗する（アンタゴニスト活性）．

(Hirose T *et al*, 2005[1]より改変引用)

アゴニスト活性を示し，このこともアリピプラゾールの臨床効果に関連している可能性がある．

DPA型抗精神病薬の臨床的特徴

これまで実施された二重盲検比較試験の結果[3]より，アリピプラゾールは統合失調症の急性増悪期の陽性および陰性症状を改善し，また長期試験において再発予防効果があることが確認されている．第1世代抗精神病薬と比較してアカシジアなどの錐体外路系副作用が少なく，他の第2世代抗精神病薬とくらべても血中プロラクチンの上昇やQTc間隔の延長が少ない．過鎮静や抗コリン性副作用（口渇や便秘）も比較的少なく，耐容性にすぐれている．ただ，前薬に強いドパミンD_2受容体遮断作用を有する抗精神病薬が投与されている患者では，アリピプラゾールへ切り替える際，一過性に精神病症状の増悪がみられることがある．

(黒木俊秀)

〔同義語〕
アリピプラゾール
ドパミン受容体部分作動薬

〔関連語〕
第2世代抗精神病薬（second-generation antipsychotics）
非定型抗精神病薬（atypical antipsychotics）
ドパミンD_2自己受容体

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Attitude of Patients With Mood Disorder Toward Clinical Trials in Japan

To the Editors:

Some attitude surveys regarding clinical trials have been conducted for the general population, outpatients, and participants in clinical trials. However, in most such surveys, the target subjects tended to be patients with some physical diseases. To our knowledge, despite a very high prevalence of depressive disorders in the general population, few attitude surveys have so far been reported for patients with such a condition. Although a placebo-controlled trial (PCT) has been generally considered desirable for the development of new antidepressants,[1] in Japan, PCTs are rarely conducted at the present time. It is also known that the subject group may not represent a standard patient population. Therefore, to promote and conduct better PCT, it is necessary to investigate the attitudes of patients with mood disorders toward clinical trials.

Patients between the age of 20 and 75 years were recruited from Kyushu University Hospital, Keio University Hospital, or University Hospital of Occupational and Environmental Health. All were outpatients diagnosed to have mood disorders—including depressive disorders, bipolar disorders, and other mood disorders—based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. After a complete description of the study, the attitudes of patients toward clinical trials were thus investigated. The patients were asked to complete a multiple choice–type questionnaire developed to survey the patients' attitudes concerning participation in PCT. This questionnaire was developed by the committee for clinical trials of the Japanese Society of Biological Psychiatry.

Seventy-seven patients (31 men and 46 women) with mood disorders were anonymously investigated. The mean ± SD age was 42.9 ± 14.3 years. Thirty-one (40.3%) of the patients knew that clinical trials had previously been conducted for the development of new drugs, 17 (22.1%) knew the word *placebo*, and 14 (18.2%) knew that PCT had previously been conducted for a strict assessment of the efficacy of various drugs. Most of the patients (16 of 17) with any knowledge of the word *placebo*, however, knew the word *placebo effect*. For 42 patients with some knowledge of clinical trials, the most frequent opinions about clinical trials were as follows: (1) clinical trials were necessary for the development of new drugs, (2) they were afraid of possible adverse effects, and (3) it was good that participants were able to contribute to the development of new drugs. After the explanation of PCT to all patients, the most frequent opinions about PCT were as follows: (1) clinical trials were necessary for the development of new drugs, (2) they were afraid of possible adverse effects, and (3) they felt unpleasant because it seemed like an experiment.

Fifteen (19.5%) of the patients stated that they would participate in PCT, whereas 27 (35.1%) stated that they might participate a little and 30 (39.0%) stated that they did not want to participate at all. There were no significant associations between the attitude for participation in PCT and knowledge about clinical trials (Fisher exact test, $\chi^2 = 3.44$, $df = 6$, $P = 0.75$) or *placebo* (Fisher exact test, $\chi^2 = 3.89$, $df = 6$, $P = 0.69$) or PCT (Fisher exact test, $\chi^2 = 0.71$, $df = 6$, $P = 0.99$).

The most frequent reasons why patients did not want to participate in PCT were as follows: (1) they were afraid that their disease status might worsen, (2) the uncertain effect of drug, (3) they were satisfied with existing drugs, and (4) they were afraid of taking a placebo. For 29 patients unwilling to participate in PCT because of fears that their disease status might worsen, 11 of the patients said they would participate in PCT if they were checked and nursed intensively. Second, for 20 patients unwilling to participate in PCT with uncertain effects of the drug as the reason, 10 of the patients said they would participate in PCT if the effect of a trial drug was clearly superior to existing drugs. Third, for 14 patients unwilling to participate in PCT with the reason that they were satisfied with existing drugs, 4 of the patients said they would participate in PCT if existing drugs were not effective enough against severe diseases. Last, for 13 patients unwilling to participate because of fears related to taking a placebo, 2 of the patients said they would participate in PCT if the probability of taking a placebo was lower.

In our survey, the most frequent opinion about clinical trials and PCT was that they were necessary for the development of new drugs, and the most frequent reason why patients did not want to participate in such studies was that they were afraid that their disease status might worsen. In other psychiatric diseases, answers about PCT were similar to the results of our study. For example, in a study of 100 patients with schizophrenia or schizophreniform disorder,[2] the most frequent motivation to participate in PCT was that PCT was needed to develop new drugs, and the most frequent reason for their unwillingness was that patients were afraid of not receiving medication, thus resulting in a worsening in their disease status or a slowing down in their recovery. In terms of patients with physical diseases or healthy general people, however, the attitudes to PCT were somewhat different in comparison with those with psychiatric diseases. For example, in

hypertensive patients,[3] the most frequent motivation for PCT was personal health benefits. In a survey by Cassileth et al,[4] most of the subjects (71%) responded that patients should serve as research subjects for clinical trials because of the potential benefit to others and the opportunity to increase their scientific knowledge. When they were supposed to actually participate in clinical trails, many subjects stated that they could receive highly advanced medical care as their reason for participation. However, differences in the contents of the questionnaire may also account for such reported attitudes, and it will be necessary to use the same questionnaire on PCT to accurately compare the subjects with psychiatric and physical diseases.

In general, clinical trials include problems related to selection bias for the subjects evaluated. In psychiatric disease, Hummer et al[2] reported that more than 50% of the patients were not willing to give their consent to a potential PCT, thus raising doubts about the generalization of data obtained by PCT. Amori and Lenox[5] reported that symptomatic volunteers for drug research tended to be sadder, more discouraged, and less interested in others than were patients drawn from normal clinical practice. In addition, depressive disorder patients have been reported to prefer psychotherapy to antidepressant treatment.[6] In a randomized trial on antimanic treatment, Licht et al[7] reported a significant difference in the symptoms between randomized patients and excluded patients.

Currently, PCTs are difficult to conduct in Japan, and the Japanese public requires more education about such clinical research before it will be feasible to conduct PCT. Our finding regarding the attitude of the patients with mood disorders toward clinical trials may help researchers to perform better PCTs in the future by including more generalized and less biased subjects.

Shougo Hirano, MD*
Toshiaki Onitsuka, MD, PhD*
Toshihide Kuroki, MD, PhD*
Kenjiro Yokota, MD, PhD*
Teruhiko Higuchi, MD, PhD†
Koichiro Watanabe, MD, PhD‡
Jun Nakamura, MD, PhD§
Shigenobu Kanba, MD, PhD*
*Department of Neuropsychiatry
Graduate School of Medical Sciences
Kyushu University
Fukuoka, Japan
†Musashi Hospital, National Center of
Neurology and Psychiatry
‡Department of Neuropsychiatry
School of Medicine
Keio University
Tokyo, Japan
and §Department of Psychiatry
University of Occupational
and Environmental Health
Fukuoka, Japan
shhirano@npsych.med.kyushu-u.ac.jp

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Dissociable contributions of MRI volume reductions of superior temporal and fusiform gyri to symptoms and neuropsychology in schizophrenia ☆

Paul G. Nestor [a,c,*], Toshiaki Onitsuka [b,c], Ronald J. Gurrera [c], Margaret Niznikiewicz [c], Melissa Frumin [b,c], Martha E. Shenton [b,c], Robert W. McCarley [c]

[a] *Department of Psychology, University of Massachusetts, Boston, United States*
[b] *Surgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States*
[c] *Clinical Neuroscience Division, Laboratory of Neuroscience, Boston VA Health Care System-Brockton Division, Department of Psychiatry, Harvard Medical School, Boston, MA, United States*

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Abstract

We sought to identify the functional correlates of reduced magnetic resonance imaging (MRI) volumes of the superior temporal gyrus (STG) and the fusiform gyrus (FG) in patients with chronic schizophrenia. MRI volumes, positive/negative symptoms, and neuropsychological tests of facial memory and executive functioning were examined within the same subjects. The results indicated two distinct, dissociable brain structure-function relationships: (1) reduced left STG volume-positive symptoms-executive deficits; (2) reduced left FG-negative symptoms-facial memory deficits. STG and FG volume reductions may each make distinct contributions to symptoms and cognitive deficits of schizophrenia.

Keywords: Schizophrenia; MRI; Neuropsychology; Symptoms

1. Introduction

The superior temporal gyrus (STG) and the fusiform gyrus (FG) are two functionally distinct regions, which are among the several brain areas that have been identified as showing reduced volumes in magnetic resonance imaging (MRI) studies of patients with schizophrenia (Onitsuka et al., 2003, 2004, 2005). Each of these areas may be linked to different facets of the well-known heterogeneous expression of schizophrenia. For example, reduced left STG volume has been linked to positive symptoms of auditory hallucinations (Barta et al., 1990; Gaser et al., 2004) and thought disorder (Shenton et al., 1992; McCarley et al., 1993) as well as to neuropsychological executive deficits (Nestor et al., 1993). In contrast, reduced left FG volume has been associated with both poor facial recognition (Onitsuka et al., 2003) and introversion, consistent

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* Corresponding author. Department of Psychology, University of Massachusetts-Boston, Boston, MA 02125-3393, United States. Tel.: +1 617 287 6387.
E-mail address: paul.nestor@umb.edu (P.G. Nestor).

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with negative symptom descriptors of social withdrawal (Onitsuka et al., 2005). Whether these structural-functional relationships can be dissociated within the same subjects is, however, unknown, as these prior studies have mainly examined behavioral correlates of STG and FG across different patient samples.

The current study thus aimed to extend these previous findings by examining and comparing within the same subjects functional correlates of reduced STG and FG volumes. Based on previous studies, we predicted STG and FG would each make distinct and specific contributions to different aspects of the phenotype of schizophrenia, as expressed in symptoms and neuropsychological test performance. To wit, reduced left STG volume is hypothesized to correlate with both positive symptoms and neuropsychological executive deficits, but not with negative symptoms and facial memory deficits, which are both hypothesized to correlate only with reduced left FG.

2. Method

2.1. Participants

Subjects were 22 medicated male patients, who had prior high-spatial resolution MRI gray matter studies of the STG (Onitsuka et al., 2003) and the FG (Onitsuka et al., 2004, 2005), and who were between the ages of 17 and 55 years (Mean=41.43 years, SD=8.22), right-handed, native speakers of English, without histories of electroconvulsive therapy or neurological illness, and without alcohol or drug abuse in the past 5 years, as assessed by the Addiction Severity Index (McLellan et al., 1992). Recruited from the VA Boston Healthcare System, Brockton Campus, patients were diagnosed with schizophrenia using the Structured Clinical Interview for DSM-IV Axis-I Disorder–Patient Edition (SCID-P) (First et al., 1997). Mean chlorpromazine equivalent daily dose was 576 mg (SD=257) (Stoll unpublished, 2003), with 12 patients taking atypical medication, 9 typical medication, and one received both. The mean duration of illness was 20.7 years (SD=8.5).

2.2. Measures

The Positive and Negative Syndrome Scale (PANSS) provides objective ratings of various positive and negative symptoms (Kay et al., 1986). The neuropsychological tests included measures of executive functioning, the Wisconsin Card Sorting Test (WCST), and delayed facial recognition, as assessed by the Faces II subtest of the Wechsler Memory Scale (WMS-III).

The MRI protocol, described in detail in other published studies (Onitsuka et al., 2003, 2004), acquired MR images with a 1.5-T General Electric scanner (GE Medical Systems, Milwaukee) at the Brigham and Women's Hospital in Boston (see Fig. 1). Manual drawings of the FG were performed on the coronal plane, blind to diagnoses (control data were not examined in this study). The anterior landmark was reliably defined by one slice posterior to the mamillary body, and the posterior landmark was determined by the anterior tip of the parietal-occipital sulcus in the mid-sagittal plane. The last slice including the crux of the fornix provided the boundary for subdivision of FG into anterior and posterior. The collateral sulcus was used as the medial border. The occipital-temporal sulcus was used to determine the lateral border. Inter-rater reliability was computed for the FG by 3 independent raters who were blind to group membership. The intra-class correlations were: 0.94 for left anterior FG, 0.94 for the right anterior, 0.95 for the left posterior, 0.95 for the right posterior. For the STG, the anterior boundary was defined as the first slice containing the intact temporal stem. The posterior landmark was determined by the last slice including the crux of the fornix. Superior temporal sulcus was used as the inferior border. Inter-rater reliability was computed for the STG by 3 independent

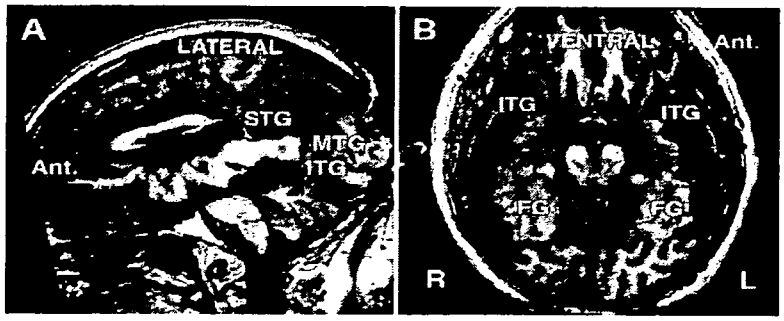

Fig. 1. Superior temporal gyrus (blue), middle temporal gyrus (tan), inferior temporal gyrus (purple), and fusiform gyrus (green) from lateral (a) and ventral (B) views.

raters, blind to group membership. The intra-class correlations for inter-rater reliability were: 0.97 for left STG, 0.98 for right STG.

3. Results

Table 1 presents symptom and neuropsychological correlates of STG and FG volumes. As shown in Table 1, reduced left FG volume correlated significantly with higher negative symptoms (rho=−.439, $p<.05$) but not with positive symptoms. In contrast, reduced left STG volume correlated significantly with higher positive symptoms (rho=−.494, $p<.05$) but not with negative symptoms. The strongest correlations among the specific symptom items were for the negative symptom emotional withdrawal and left FG volume (rho=−.467, $p<.05$), and for the positive symptom hallucinations and left STG (rho=−.613, $p<.01$). For the neuropsychological scores, reduced left FG also correlated significantly with lower scores for facial memory (rho=.609, $p=.01$), whereas reduced left STG volume correlated significantly with increased non-perseverative WCST errors, a measure of executive functioning (rho=−.479, $p<.05$). Neither positive symptoms nor negative symptoms correlated significantly with neuropsychological scores for facial memory or executive functioning.

Table 1
Spearman Rank correlations of MRI volumes with symptom ratings and neuropsychological scores

Brain area	Symptom ratings		Neuropsychological scores	
	Positive symptoms	Negative symptoms	Non-perseverative errors[a]	Facial memory[b]
Fusiform gyrus				
Right	.070	−.336	−.053	.588*
Anterior	.089	−.216	.248	.543*
Posterior	.042	−.259	−.148	.364
Left	.191	−.439*	−.001	.609*
Anterior	.173	−.301	.421	.579*
Posterior	.144	−.368	−.201	.354
Superior temporal gyrus				
Right	.289	−.047	.560**	−.351
Anterior	.149	−.203	−.250	−.315
Posterior	.470*	.004	−.492*	.343
Left	.494*	−.048	−.479*	−.290
Anterior	−.083	.099	−.066	−.127
Posterior	−.564**	−.186	−.432*	−.272

**$p<.01$, *$p<.05$.
[a] Non-perseverative errors on the Wisconsin Card Sorting Test.
[b] Faces II scores on the Weschler Memory Scale-III.

We next used hierarchical multiple regression to compare, quantify, and parse these significant functional correlates of the FG and the STG. For negative symptoms, reduced left FG volume emerged as the sole contributor, accounting for 23% of the variance in negative symptoms, ($F=5.75$, $df=1, 20$, $p<.05$); posterior and anterior segments of the left FG did not account for any significant variation in negative symptoms. By comparison, reduced left STG volume accounted for 19% of the variance in positive symptoms ($F=4.63$, $df=1, 20$, $p<.05$), with reductions of the left posterior STG volume making an even greater contribution, accounting for 25% of the variance in positive symptoms ($F=6.48$, $df=1, 20$, $p<.05$). For neuropsychological correlates, reductions of the left anterior FG contributed significantly to lower facial memory scores, accounting for 33% of the variance ($F=6.80$, $df=1, 14$, $p<.05$). Similarly, left posterior STG volume accounted for 22% of the variance in errors in executive functioning, ($F=5.27$, $df=1, 19$, $p<.05$).

4. Discussion

We compared within the same subjects with schizophrenia functional correlates of reductions in the STG and the FG. The results suggested that the STG and the FG may each account for different facets of the schizophrenic phenotype, as expressed in symptoms and neuropsychological test performance. That is, as predicted, the results pointed to two distinct, dissociable brain structure–function relationships: (1) reduced left STG volume–positive symptoms–executive deficits; (2) reduced left FG–negative symptoms–facial memory deficits. Seldom have patterns of correlations provided such clear evidence as in the current study of a double dissociation of anatomy and function in schizophrenia as reflected by the non-overlapping reduced left STG volume with positive symptoms and executive deficits versus reduced left FG volume with negative symptoms and facial memory deficits.

The current study integrated neuroimaging, neuropsychology, and symptom ratings so as to parse the different facets of the well-known heterogeneous phenotype of schizophrenia, and to understand better its social and cognitive consequences. As such, the current findings may add to the future social-cognitive neuroscience study of schizophrenia. However, schizophrenia affects diverse areas of the brain, and future studies are needed that use a broader sampling of brain regions in unselected group of patients, preferably unmedicated, with a wider range of length of illness than those of the present investigation.

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Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study

Toshiaki Onitsuka [a,b], Robert W. McCarley [a], Noriomi Kuroki [a], Chandlee C. Dickey [a,d], Marek Kubicki [a,c,d], Susan S. Demeo [a], Melissa Frumin [a], Ron Kikinis [c], Ferenc A. Jolesz [c], Martha E. Shenton [a,c,d,*]

[a] *Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, Boston VA Healthcare System, Brockton Division and Harvard Medical School, Brockton, MA, United States*
[b] *Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[c] *Surgical Planning Laboratory, Brigham and Women's Hospital, Department of Radiology, Harvard Medical School, Boston, MA, United States*
[d] *Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Department of Psychiatry, Harvard Medical School, Boston, MA, United States*

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Abstract

Schizophrenia is characterized by deficits in cognition as well as visual perception. There have, however, been few magnetic resonance imaging (MRI) studies of the occipital lobe as an anatomically defined region of interest in schizophrenia. To examine whether or not patients with chronic schizophrenia show occipital lobe volume abnormalities, we measured gray matter volumes for both the primary visual area (PVA) and the visual association areas (VAA) using MRI based neuroanatomical landmarks and three-dimensional information. PVA and VAA gray matter volumes were measured using high-spatial resolution MRI in 25 male patients diagnosed with chronic schizophrenia and in 28 male normal controls. Chronic schizophrenia patients showed reduced bilateral VAA gray matter volume (11%), compared with normal controls, whereas patients showed no group difference in PVA gray matter volume. These results suggest that reduced bilateral VAA may be a neurobiological substrate of some of the deficits observed in early visual processing in schizophrenia.

Keywords: High-spatial resolution MRI; Schizophrenia; Primary visual area; Visual association areas; Quantitative MRI

1. Introduction

Schizophrenia is characterized by deficits in cognition as well as visual perception (O'Donnell et al., 1996; Tek et al., 2002). Deficits in early visual processing have been repeatedly reported (Doniger et al., 2002; Keri et al., 2004; Butler et al., 2001, 2005), and recent electroencephalographic (EEG) studies provide further evidence for deficits in early visual processing in schizophrenia (Doniger et al., 2002; Butler et al., 2001, 2005). With respect to clinical symptoms, patients with schizophrenia sometimes evince visual hallucinations, which are associated with activity in

* Corresponding author. Psychiatry Neuroimaging Laboratory, Department of Psychiatry, 1249 Boylston Street, Boston, MA 02215, United States. Tel.: +1 617 525 6117; fax: +1 617 525 6150.
E-mail address: Shenton@bwh.harvard.edu (M.E. Shenton).

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the visual association cortex (Silbersweig et al., 1995). Of note here, Weiss and Heckers (1999) noted that the neural systems involved in the perception of hallucinations appears to involve the same modality-specific cerebral structures as are involved in normal perception. Recently, Molina et al. (2005) reported that clozapine increased occipital lobe metabolism including primary and association visual areas, and that the metabolic increase was associated with improvement of positive symptoms. Our own laboratory has documented that visual gestalt stimuli lead to abnormal gamma band EEG activity over the occipital lobe in schizophrenia, and that this abnormal gamma activity is associated with visual hallucinations (Spencer et al., 2003, 2004). It thus seems likely that the occipital lobe is involved in some aspects of the pathophysiology of schizophrenia.

Magnetic resonance imaging (MRI) has been helpful in revealing subtle structural brain abnormalities in schizophrenia (see reviews in McCarley et al., 1999; Shenton et al., 2001) although the small number of studies that have measured occipital lobe have shown mixed findings. Five studies reported volume reduction in the occipital lobe in schizophrenia (Zipursky et al., 1992; Andreasen et al., 1994; Bilder et al., 1994, 1999; Davatzkikos et al., 2005). However, differences in methodology and regions of interest (ROI) definition may have accounted for some of the disparate results. In terms of neuroanatomically defined studies of occipital lobe, Zipursky et al. (1992) used seven axial MRI sections for segmentation and found significant gray matter volume reduction in the occipital lobe in patients. On the other hand, Goldstein et al. (1999) reported no group differences between patients with schizophrenia and controls in the occipital lobe. For voxel-based morphometric (VBM) studies, Davatzkikos et al. (2005) reported reduced gray matter in occipital association areas in patients with schizophrenia, although there have also been negative findings reported using VBM (e.g., Kubicki et al., 2002; Giuliani et al., 2005).

Based on direct comparisons of VBM and ROI, we (Kubicki et al., 2002) and Giuliani et al. (2005) concluded that VBM is useful for hypothesis generation, but that its anatomical warping and density-based methodology often lead to failure to detect abnormalities seen using ROI analysis. In the present study we adopted a neuroanatomically defined and manually delineated ROI method to evaluate occipital lobe ROI.

One possible reason for the small number of neuroanatomically defined ROI studies may be due to difficulties in defining occipital lobe boundaries. The boundary between the occipital lobe and parietal lobe, the parietooccipital sulcus (POS), clearly separates the two lobes on the medial surface (Duvernoy, 1991). However, on the lateral surface, these two lobes are usually divided with a (theoretical) line starting at the parietooccipital fissure and extending to the temporo-occipital incisure (Duvernoy, 1991). In the present study, we used three-dimensional information to provide reliable measures of the occipital lobe with a software package for medical image analysis [3D slicer, http://www.slicer.org] on a workstation.

For ROI studies, it is important to separate gray and white matter in the analysis. This approach can improve the detection of subtle gray matter volume differences between groups, since white matter volume may be relatively intact as reported in several MRI studies of frontal and temporal lobes in schizophrenia (e.g., Gur et al., 2000; Hirayasu et al., 2001). Thus, in the present study, we used a fully-automated segmentation program (Wells et al., 1996) to classify tissue into gray matter, white matter, and cerebral spinal fluid (CSF). Finally, consideration must be given to linking neuroanatomically defined ROI to functional divisions whenever possible (e.g., delineation for Heschl's gyrus, the locus of primary auditory cortex [Hirayasu et al., 2000]). For the occipital lobe, the cytoarchitecture changes abruptly at the border between Brodmann areas 17 and 18, with especially prominent changes in layer IV, which becomes thinner and less differentiated in area 18 than in area 17 (Amunts et al., 2000). Although structural MRI cannot identify this border, functional neuroimaging studies have reported that the primary visual area in humans is distributed approximately one gyrus above and below the calcarine fissure (Tootell et al., 1996; Van Essen and Drury, 1997). We therefore decided to use this ROI definition to delineate these regions; for convenience we will refer to the (mainly) primary visual area as PVA and the (mainly) visual association area as VAA, comprising the non-PVA portions of the occipital lobe. Our use of designations other than Brodmann areas and those in use in anatomical studies will also serve to indicate the tentative functional identification of PVA and VAA.

The principal aim of this study was to measure PVA and VAA gray matter volumes in chronic schizophrenia and normal comparison subjects, using high spatial resolution MRI (0.9375-mm^3 voxels in resampled slices) and three-dimensional information, in order to provide more reliable measurement of these brain regions, as well as to determine whether or not there are differences between groups. We also investigated associations between clinical symptoms and gray

matter volumes of PVA and VAA in the patient sample, where we predicted that increased severity of visual hallucinations would be significantly associated with reduced occipital gray matter volumes.

2. Subjects and methods

2.1. Subjects

Twenty-five male patients with chronic schizophrenia and 28 male normal control subjects participated in this study. Subjects included 2 new subjects and 49 subjects common (23 patients and 28 normal controls) to our most recently published ROI study in chronic schizophrenia (Onitsuka et al., 2004) (the study reported reduced left middle inferior temporal and bilateral inferior temporal gyri gray matter volumes in schizophrenia). After a complete description of the study, written informed consent was obtained from all participants. The age range for inclusion was 20 to 55 years. Subjects were included if they had no history of: 1) neurologic illness or major head trauma; 2) electroconvulsive therapy; 3) alcohol or drug dependence; or 4) alcohol and drug abuse within the past 5 years. Table 1 shows demographic and clinical characteristics of study groups.

Normal control subjects were recruited through newspaper advertisement and screened using the Structured Clinical Interview (SCID non-patient edition) by trained interviewers (MES, MF). No control subjects had an Axis-I psychiatric disorder or a first-degree relative with Axis-I psychiatric disorder. The mean age of the normal control group was 42.0±7.5 (mean±SD) years (range: 28–55).

All patients were diagnosed with schizophrenia based on DSM-IV criteria, using information from the Structured Clinical Interview for DSM-III-R by the same trained interviewers. Patients were recruited from the VA Boston Healthcare System, Brockton Division. All patients were receiving neuroleptic medication, with a mean daily dose equivalent to 497±258 mg of chlorpromazine [typical (9 of the 25 patients), atypical (15), or both (1)]. The mean age of patients was 42.6±8.4 years (range: 29–55), their mean age at symptom onset was 22.7±4.1 years, and their mean duration of illness was 19.9±9.6 years. The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) were administered to patients. Mean+SD SAPS and SANS scores were 9.2±3.7 and 12.3±3.9, respectively. For the SAPS, visual hallucination scores (0=none, 5=severe) were available in sixteen of the twenty-five patients. Mean±SD score was 1.3±1.5 (range 0–4).

Handedness was assessed using the Edinburgh inventory. Socioeconomic status (SES) of subjects and parental SES were measured by the Hollingshead two-factor index (1=highest, 5=lowest). All subjects were given the WAIS-R information subscale as an estimate of gross fund of information. *t*-tests were used to assess group differences in age, handedness score, SES, parental SES and WAIS-R information subscale scores. There were no significant group differences in age, handedness score, parental SES or WAIS-R information subscale (see Table 1). Patients with schizophrenia showed significantly lower SES than normal control subjects ($t[51]=-7.82$, $p<0.001$), consistent with reduced functioning due to the disorder.

Table 1
Demographic and clinical characteristics of study groups

	Patients with schizophrenia (N=25)	Normal controls (N=28)	df	t	p
Total ICC (ml)	1513.8±105.6	1566.4±140.7	51	1.52	0.134
Age (range)	42.6±8.4 (29–55)	42.0±7.5 (28–55)	51	−0.27	0.787
Handedness	0.78±0.16	0.80±0.18	51	0.52	0.603
SES[a]	4.1±0.7	2.0±1.1	51	−7.82	<0.001*
Parental SES	2.9±1.4	2.5±1.0	51	−1.14	0.262
WAIS-R, information subscale	10.1±2.6	11.0±1.8	51	1.56	0.126
Medication dose[b] (CPZ equiv., mg)	497±258				
Symptom onset (years)	22.7±4.1				
Duration of illness (years)	19.9±9.6				
SAPS total	9.2±3.7				
SANS total	12.3±3.9				

* Patients with schizophrenia showed significantly lower SES than controls.

[a] Higher scores indicating lower SES.

[b] Patients were administered the following medications: [N=5 risperidone, N=4 haloperidol, N=3 ziprasidone; N=3 fluphenazine; N=3 clozapine, N=2 olanzapine; N=1 perphenazine; N=1 chlorpromazine; N=1 olanzapine and ziprasidone; N=1 quetiapine and olanzapine; N=1 risperidone and chlorpromazine].

2.2. MRI procedures and definition of occipital lobe

The acquisition was done with a 1.5-tesla General Electric scanner (GE Medical Systems, Milwaukee) at the Brigham and Women's Hospital in Boston. The protocol followed that of our previous publication (Onitsuka et al., 2004).

Fig. 1 shows the medial and lateral view of the three-dimensional reconstruction of the occipital lobe. The following steps were used to define the occipital lobe. First, the parietooccipital sulcus (POS) was identified on the midsagittal plane for each hemisphere. Second, the anterior tip of the POS was identified, as well as the posterior tip of the POS that corresponds to the parietooccipital fissure (see Fig. 1). The occipital lobe was defined as beginning at one slice posterior to the plane that contains the anterior tip of the POS, identified on the midsagittal plane, and ending in the last slice in the coronal plane, including the posterior tip of occipital lobe. For the medial surface, the boundary between the parietal and occipital lobe was the POS. For the lateral surface, the rater (TO) drew a guideline connecting the parietooccipital fissure and the superior temporal sulcus, or anterior occipital sulcus, on the first, beginning slice of occipital lobe. This guideline was defined as the boundary between the parietal and occipital lobe for the lateral surface. This guideline was seen as a point on each coronal image (see Fig. 2c). The parietal and occipital lobe were divided operationally by extending the guideline across the tissue bridge of white matter, horizontally and medially up to the intraparietal sulcus (see Fig. 2c and d).

The primary visual area (PVA) was defined as the area between one gyrus above the calcarine fissure and one gyrus below the sulcus on each coronal image. The rater drew two guidelines at 3–5 slices laterally from the medial surface to determine the gyri above and below calcarine fissure (see Fig. 2b). The lines were drawn extending the sulcal course across the tissue bridge of white matter. These guidelines were seen as points on each coronal image and the rater delineated the primary visual area referring to the lines (see Fig. 2c). Manual drawings of the ROIs were then performed on the realigned and resampled coronal slices (see Fig. 2d).

Interrater reliability was computed for the ROIs by 3 independent raters (TO, NK, and SSD), who were blinded to diagnostic group membership. Six cases were selected randomly for interrater reliability. Three raters measured the occipital lobe on every third slice. An intraclass correlation coefficient was used to compute interrater reliability. For the three raters, the intraclass correlations were: 0.93 for the left PVA, 0.90 for the right PVA, 0.98 for the left VAA, 0.98 for the right VAA.

2.3. Statistical analyses

A *t*-test was used to assess group differences in total ICC. There was no significant group difference in total ICC ($t[51]=1.52$, $p=0.13$). However, to correct for variations in brain size, we used relative volumes of PVA

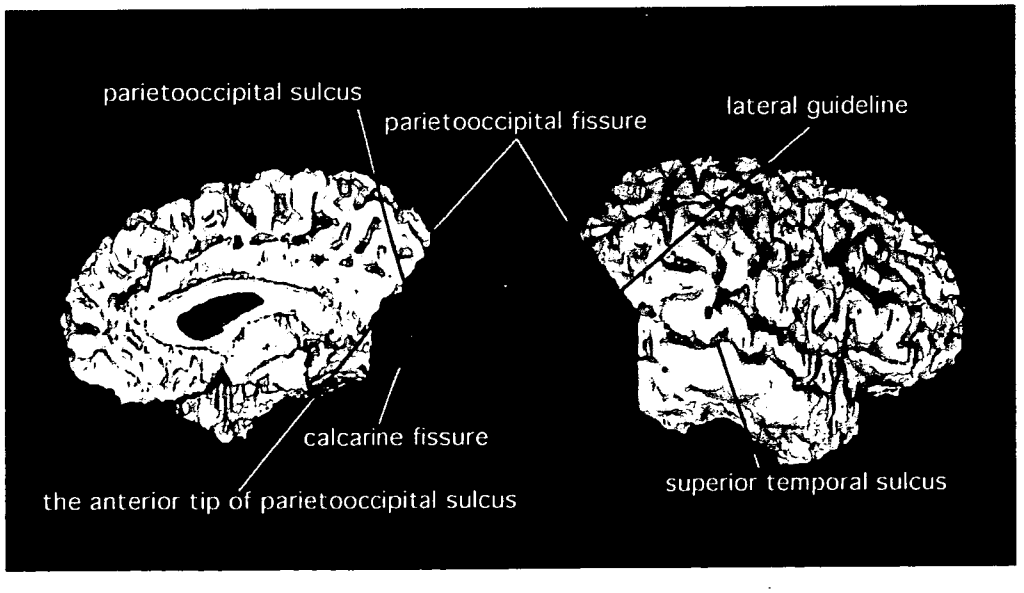

Fig. 1. Delineation of PVA and VAA in occipital lobe. PVA is shown in purple, and VAA is shown in blue. For the medial surface (left), the border between parietal lobe and occipital lobe is the parietooccipital sulcus. PVA is defined as the area including one gyrus above and one gyrus below the calcarine fissure. For the lateral surface (right), the border between the two lobes is delineated by a guideline connecting the parietooccipital fissure and the superior temporal sulcus on the most anterior slice of occipital lobe (The guideline is shown in red).

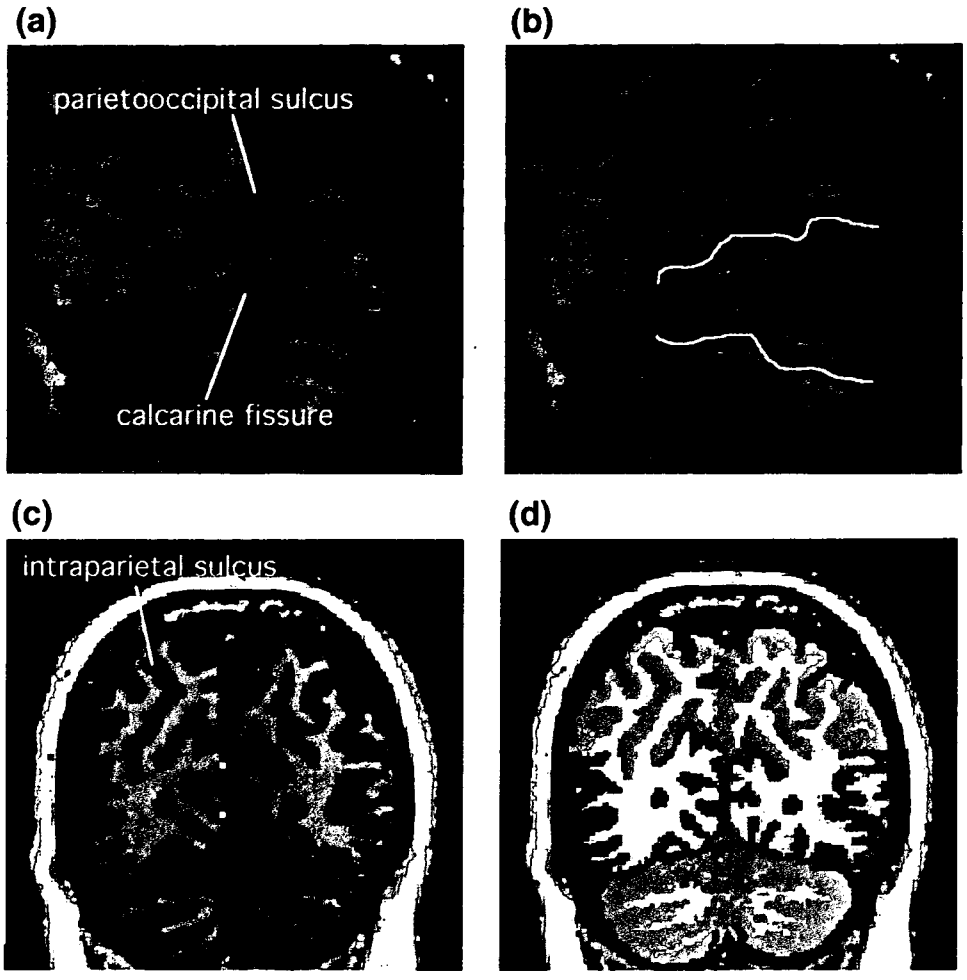

Fig. 2. Sagittal and coronal MR images showing delineation of PVA and VAA. (a) The rater identifies the parietooccipital sulcus and the calcarine fissure on the midsagittal plane. (b) The yellow lines are the guidelines extending the sulcal courses used to delineate PVA and VAA. (c) On a coronal slice PVA and VAA are delineated by referring to the guidelines (yellow dots). In part B, here shown as yellow dots. On the lateral surface, the parietal lobe and occipital lobe are operationally separated by extending the guideline (the red dot) horizontally and medially across the tissue bridge of white matter horizontally and medially up to the intraparietal sulcus. (d) A coronal view of PVA and VAA delineation. White matter and gray matter were shown in light yellow and light blue respectively. The gray matter of PVA is shown in orange (subject left) and purple (subject right). The gray matter of VAA is shown in red (subject left) and blue (subject right).

and VAA computed as [(absolute volume)/(ICC)] × 100 for ROI analysis. To examine whether or not the ROI volumes were normally distributed, Shapiro–Wilk tests (Shapiro and Wilk, 1965) were performed for each ROI in both groups. To determine whether or not certain ROIs were more affected than other ROIs, the ROI volumes were first converted to *Z*-scores so that all the ROIs would be on the same scale. The mean and standard

Table 2
Mean±SD absolute (ml) and relative volume (%) for occipital lobe gray matter in chronic schizophrenia and normal controls

	Patients with Schizophrenia (N=25)	Normal Controls (N=28)	t	df	p
Total ICC (ml)	1513.8±105.6	1566.4±140.7	1.52	51	0.134
Left primary visual area	5.65±1.00	5.93±1.03	0.98	51	0.330
	(0.37±0.06)	(0.38±0.07)	0.37	51	0.717
Left visual association area	19.06±4.40	22.26±5.16	2.42	51	0.019
	(1.26±0.28)	(1.42±0.31)	2.01	51	0.049
Right primary visual area	5.57±0.91	5.79±1.23	0.72	51	0.477
	(0.37±0.05)	(0.37±0.08)	0.16	51	0.874
Right visual association area	18.96±4.37	21.94±5.18	2.24	51	0.029
	(1.25±0.27)	(1.40±0.31)	1.90	51	0.064

Relative volumes (% total ICC) are in parentheses. Statistical significance levels are computed using t-tests.

deviation of the control group were used to calculate the *Z*-scores. For ROI analysis, the standardized scores were submitted to a mixed model repeated measure ANOVA with group (schizophrenia or controls) as a between-subjects factor, and hemisphere (left or right) and subdivision (PVA or VAA) as within-subjects factors.

Exploratory analyses were performed, using Spearman's rho, to explore the relationship between volumes for each ROI, and demographic data, the SAPS and SANS total scores, as well as for SAPS visual hallucination scores. Here, all correlations were considered significant only if they reached $p \leq 0.05$ (two-tailed), for both relative and absolute volumes.

3. Results

3.1. Volume of occipital lobe

Table 2 shows absolute and relative occipital lobe volumes of patients with schizophrenia and normal controls. For the 3-factor (2 groups × 2 sides × 2 subdivisions) ANOVA of standardized ROI values (*Z*-scores), there was a significant main effect of subdivision ($F[1,51]=4.08$, $p=0.05$, while there was no significant main effect of hemisphere ($F[1,51]=0.06$, $p=0.81$), or group ($F[1,51]=2.16$, $p=0.15$). There was also no significant hemisphere-by-subdivision-by-group

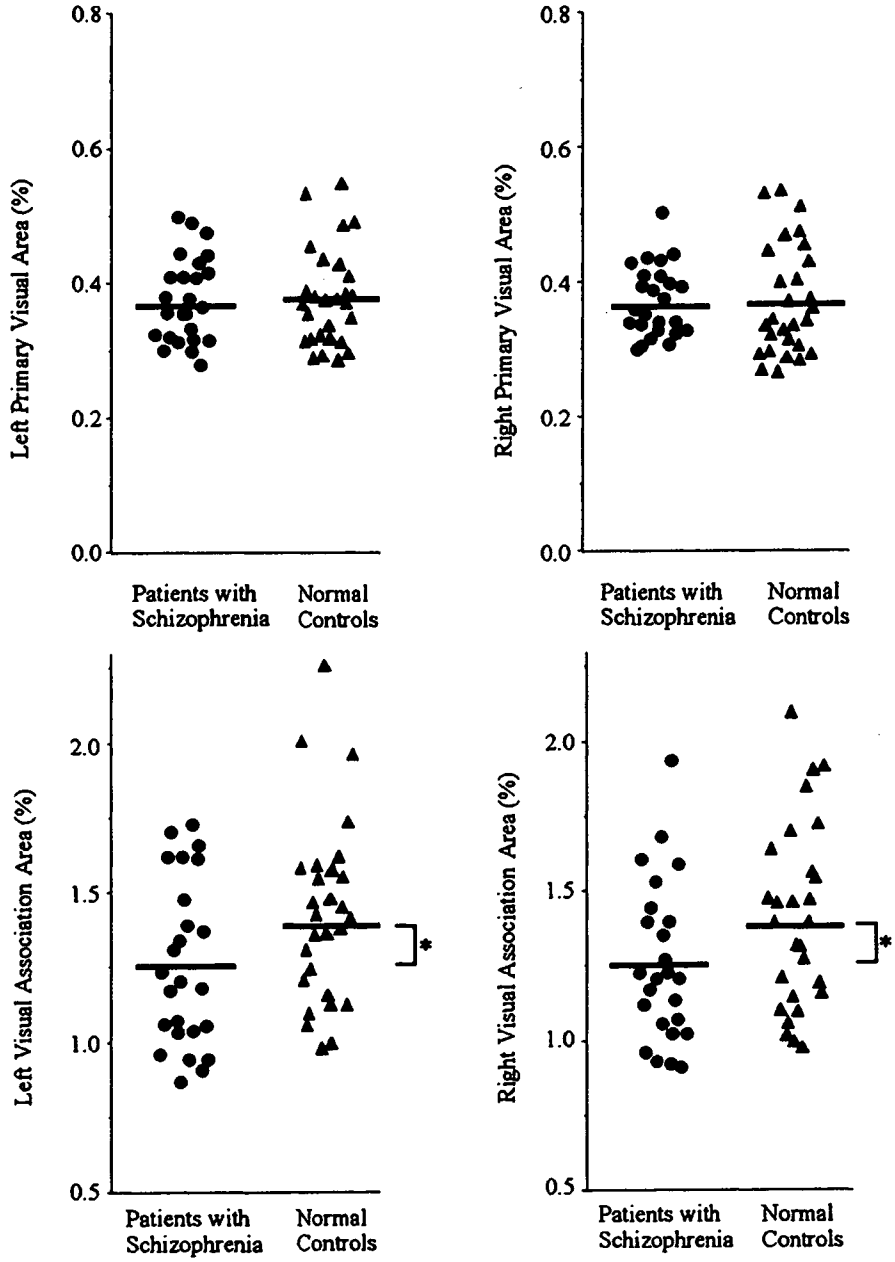

Fig. 3. Scattergram of PVA and VAA relative volumes on the left and right in patients with schizophrenia (circles) and normal control subjects (triangles). Means are indicated by horizontal lines. *Patients showed bilateral VAA reduction compared with normal controls ($F[1,51]=5.05$, $p=0.03$).

interaction ($F[1,51]=0.06$, $p=0.94$). However, there was a significant subdivision-by-group interaction ($F[1,51]=4.08$, $p=0.05$) but no significant hemisphere-by-group ($F[1,51]=0.06$, $p=0.81$) or hemisphere-by-subdivision ($F[1,51]=0.06$, $p=0.94$) interactions.

To further delineate the subdivision-by-group significant interaction, follow-up ANOVA was performed for each subdivision. For PVA, there was no significant main effect of group ($F[1,51]=0.09$, $p=0.77$) or hemisphere ($F[1,51]=0.07$, $p=0.79$), and no significant hemisphere-by-group interaction ($F[1,51]=0.07$, $p=0.79$). These results suggest that there is no group difference in PVA bilaterally.

For VAA, there was a significant main effect of group ($F[1,51]=5.05$, $p=0.03$) without a significant main effect of hemisphere ($F[1,51]=0.02$, $p=0.89$) or a significant hemisphere-by-group interaction ($F[1,51]=0.02$, $p=0.89$), indicating that patients showed bilateral VAA reduction compared with normal controls. The percentages of relative VAA reduction of patients were 11.4% for the left and 10.7% for the right (Fig. 3).

3.2. Correlations between volume of occipital lobe and demographic/clinical measurements

In normal controls, age, parental SES, SES, handedness and WAIS-R information subscale scores did not correlate significantly with occipital lobe volume ($-0.351 \leq \text{rho} \leq 0.301$, $0.07 \leq p \leq 0.98$), with the exception of a significant negative correlation between SES and right PVA volume (rho=−0.522, $p=0.004$ for absolute; rho=−0.525, $p=0.004$ for relative). In patients with schizophrenia, age, SES, parental SES, WAIS-R information subscale scores, duration of illness, and dose (chlorpromazine equivalent) of medication did not correlate significantly with occipital lobe volume ($-0.383 \leq \text{rho} \leq 0.360$, $0.07 \leq p \leq 0.98$), with the exception of a significant positive correlation between WAIS-R information subscale score and left PVA volume (rho=0.484, $p=0.01$ for absolute; rho=0.464, $p=0.02$ for relative).

In examining the relationships between occipital lobe volume and psychopathology measures, there were no significant correlations between ROIs and SAPS or SANS total scores ($-0.386 \leq \text{rho} \leq 0.097$, $0.07 \leq p \leq 0.93$). For SAPS visual hallucination scores, we found no significant correlations between the scores and left PVA volumes or left or right VAA volumes ($-0.251 \leq \text{rho} \leq 0.074$, $0.35 \leq p \leq 0.97$). However there was a significant negative correlation between right PVA volumes and visual hallucination scores (rho=−0.632, $p=0.009$ for absolute; rho=−0.617, $p=0.011$ for relative). Because of the results of Spencer et al. (2003, 2004), *t*-tests were used for additional (exploratory) analyses of ROI volume differences between the 9 patients with and the 7 patients without visual hallucinations. Of note here, there was a significant group difference in right PVA gray matter volume ($t[14]=-2.32$, $p=0.04$), although there were no significant differences in the other ROIs ($-1.15 \leq t[14] \leq -0.08$, $0.27 \leq p \leq 0.94$). For differences in demographic/clinical measurements between patients with and without visual hallucinations, there were no significant subgroup differences in chlorpromazine equivalent ($t[14]=-0.12$, $p=0.90$), age ($t[14]=-0.03$, $p=0.97$), age at symptom onset ($t[14]=1.48$, $p=0.16$), duration of illness ($t[14]=-0.80$, $p=0.44$), SES ($t[14]=-0.38$, $p=0.71$), parental SES ($t[14]=0.63$, $p=0.54$) or handedness ($t[14]=1.23$, $p=0.24$).

4. Discussion

The current study examined PVA and VAA gray matter volumes and investigated correlations between ROI volumes and clinical symptoms. For PVA gray matter volume, there was no significant group difference, while patients with schizophrenia showed significant VAA gray matter volume reduction, bilaterally, compared with healthy controls.

There are a small number of previous structural MRI studies of occipital lobe in schizophrenia. Goldstein et al. (1999), for example, used a semi-automated method of cortical parcellation to measure 48 topography defined brain regions of the entire neocortex and found no difference in occipital lobe gray matter volume between 29 patients (12 females) and 26 control subjects (14 females), although they reported the results of both genders as one group. In contrast, Andreasen et al. (1994) used an automated atlas-based dissection of specific regions without separation for gray and white matter. They reported a significant difference in occipital brain tissue volume between 36 male patients and 48 male controls, while there was no group difference in female subjects; thus gender differences in the manifestation of schizophrenia may account for the reported discrepancies in findings. In addition, differences in ROI definition and methodology may also account for the reported discrepancies. For example, Zipursky et al. (1992) used seven axial MRI sections for segmentation and found significant gray matter volume reduction in the occipital lobe in patients. More recently, Quarantelli et al. (2002) used their own automated segmentation method of major brain structures according to the Talairach atlas and found no group differences

in occipital lobe between controls and patients with schizophrenia. However a recent VBM study (Davatzikos et al., 2005) reported reduced gray matter in occipital lobe areas in patients with schizophrenia.

Another possible reason for inconsistent findings is that occipital lobe volume reduction may be just at the threshold for MRI detection, and hence whether statistical significance is found may depend heavily on the subject group evaluated. As reviewed by Shenton et al. (2001), the left superior temporal gyrus (STG) gray matter reduction is the most frequently reported MRI finding in patients with schizophrenia; thus the left STG reduction is thought to be most common affected region across individuals in schizophrenia, while occipital lobe reduction is relatively less common across individuals. Random variation in subjects may therefore account for inconsistent findings in the occipital lobe in schizophrenia.

The current study suggests that the primary visual area was relatively intact in schizophrenia compared to the association area. Pearlson et al. (1996) highlights the importance of structural abnormalities in schizophrenia in heteromodal association cortex. Our current finding that PVA did not differ between groups may partially support this hypothesis since our PVA is mainly unimodal primary sensory cortex. In a postmortem study by Selemon et al. (1995), these investigators found neuronal density increase in pyramidal layers III and V, with a trend-level cortical thickness reduction in Brodmann area 17 in patients with schizophrenia. Of note here, our current finding may not conflict completely with their finding since cortical thickness reduction was trend-level and it remains unclear how cortical thickness relates to cortical gray matter volume.

With respect to clinical correlations, although exploratory, increased severity of visual hallucinations was significantly associated with smaller right PVA volumes in patients with schizophrenia. Of further note, a recent case report of a patient with brain infarction in the right medial occipital lesion showed visual hallucinations (Beniczky et al., 2002). Moreover, there was a case report that a patient with brain infarction in the region of the calcarine fissure showed visual hallucinations (Merabet et al., 2003). Although there were no significant group differences observed for PVA gray matter volume, *t*-tests comparing the 9 patients with and the 7 patients without visual hallucinations showed a significant group difference in right PVA gray matter volume. To the best of our knowledge, our study is the first structural MRI study that indicates a significant association between the occipital lobe and visual hallucinations in patients with schizophrenia. In conjunction with findings of case reports and our results, the PVA might be crucial for visual hallucinations. However, this exploratory finding warrants confirmation in a larger sample.

In reviewing the current study, it is important to point out several possible limitations. First, the current study cannot answer the question of whether the volume reduction observed is associated with progressive in the peri- and/or post-onset course of illness, or whether it is neurodevelopmental in origin, or perhaps a combination of both. It will thus be important to investigate whether VAA gray matter volume undergoes a progressive decrease over a period of 1.5 years following first hospitalization, as we have found for superior temporal gyrus (Kasai et al., 2002). Second, the current study also did not allow us to exclude the effect of chronic treatment with neuroleptic medication on VAA gray matter abnormalities in patients (although no volume measure correlated with neuroleptic dosage), nor did we demonstrate specificity to schizophrenic psychosis, as we did not include another psychosis group. It will thus be important to investigate whether VAA abnormality is observed or not in patients with schizophrenia and affective psychosis at their first hospitalization, with minimal or no medication history. Third, this study does not provide the answer as to whether female patients show gray matter volume abnormality of VAA or not, since this study did not include any female subjects. Gender effects thus remain to be examined. Finally, an association between the occipital lobe and visual hallucinations should be confirmed in a larger sample, since visual hallucination scores were available in a part of the patients with schizophrenia of the present study.

In summary, the present study used consistent neuroanatomical boundaries for defining PVA and VAA, using three-dimensional information from MRI scans. These results suggest that patients with schizophrenia have relatively intact PVA and reduced bilateral VAA, which may be the substrate of some of the deficits observed in early visual processing.

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